

TITLECYCLIC DERIVATIVES AS MODULATORS OF CHEMOKINE
RECEPTOR ACTIVITY

5

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims the priority benefits
of U.S. Provisional Application No. 60/446,850, filed
February 12, 2003, which is expressly incorporated fully
10 herein by reference.

FIELD OF THE INVENTION

This invention relates generally to modulators
of chemokine receptor activity, pharmaceutical
15 compositions containing the same, and methods of using
the same as agents for treatment and prevention of
inflammatory diseases, allergic and autoimmune diseases,
and in particular, asthma, rheumatoid arthritis,
atherosclerosis, and multiple sclerosis, processes of
20 forming and intermediates thereof.

BACKGROUND OF THE INVENTION

Chemokines are chemotactic cytokines, of molecular
weight 6-15 kDa, that are released by a wide variety of
cells to attract and activate, among other cell types,
25 macrophages, T and B lymphocytes, eosinophils, basophils
and neutrophils (reviewed in: Luster, *New Eng. J. Med.*
1998, 338, 436-445 and Rollins, *Blood* **1997**, 90, 909-928).
There are two major classes of chemokines, CXC and CC,
depending on whether the first two cysteines in the amino
30 acid sequence are separated by a single amino acid (CXC)
or are adjacent (CC). The CXC chemokines, such as
interleukin-8 (IL-8), neutrophil-activating protein-2
(NAP-2) and melanoma growth stimulatory activity protein



(MGSA) are chemotactic primarily for neutrophils and T lymphocytes, whereas the CC chemokines, such as RANTES, MIP-1 α , MIP-1 β , the monocyte chemotactic proteins (MCP-1, MCP-2, MCP-3, MCP-4, and MCP-5) and the eotaxins (-1 and
 5 -2) are chemotactic for, among other cell types, macrophages, T lymphocytes, eosinophils, dendritic cells, and basophils. There also exist the chemokines lymphotactin-1, lymphotactin-2 (both C chemokines), and fractalkine (a CX₃C chemokine) that do not fall into
 10 either of the major chemokine subfamilies.

The chemokines bind to specific cell-surface receptors belonging to the family of G-protein-coupled seven-transmembrane-domain proteins (reviewed in: Horuk, *Trends Pharm. Sci.* **1994**, 15, 159-165) which are termed
 15 "chemokine receptors." On binding their cognate ligands, chemokine receptors transduce an intracellular signal through the associated trimeric G proteins, resulting in, among other responses, a rapid increase in intracellular calcium concentration, changes in cell shape, increased
 20 expression of cellular adhesion molecules, degranulation, and promotion of cell migration. There are at least ten human chemokine receptors that bind or respond to CC chemokines with the following characteristic
 patterns (reviewed in Zlotnik and Oshie *Immunity* **2000**,
 25 12, 121): CCR-1 (or "CKR-1" or "CC-CKR-1") [MIP-1 α , MCP-3, MCP-4, RANTES] (Ben-Barruch, et al., *Cell* **1993**, 72, 415-425, and Luster, *New Eng. J. Med.* **1998**, 338, 436-445); CCR-2A and CCR-2B (or "CKR-2A"/"CKR-2B" or "CC-CKR-2A"/"CC-CKR-2B") [MCP-1, MCP-2, MCP-3, MCP-4, MCP-5]
 30 (Charo, et al., *Proc. Natl. Acad. Sci. USA* **1994**, 91, 2752-2756, and Luster, *New Eng. J. Med.* **1998**, 338, 436-445); CCR-3 (or "CKR-3" or "CC-CKR-3") [eotaxin-1, eotaxin-2, RANTES, MCP-3, MCP-4] (Combadiere, et al., *J.*

Biol. Chem. **1995**, 270, 16491-16494, and Luster, *New Eng. J. Med.* **1998**, 338, 436-445); CCR-4 (or "CKR-4" or "CC-CKR-4") [TARC, MDC] (Power, et al., *J. Biol. Chem.* **1995**, 270, 19495-19500, and Luster, *New Eng. J. Med.* **1998**, 338, 436-445); CCR-5 (or "CKR-5" OR "CC-CKR-5") [MIP-1 α , RANTES, MIP-1 β] (Sanson, et al., *Biochemistry* **1996**, 35, 3362-3367); CCR-6 (or "CKR-6" or "CC-CKR-6") [LARC] (Baba, et al., *J. Biol. Chem.* **1997**, 272, 14893-14898); CCR-7 (or "CKR-7" or "CC-CKR-7") [ELC] (Yoshie et al., *J. Leukoc. Biol.* **1997**, 62, 634-644); CCR-8 (or "CKR-8" or "CC-CKR-8") [I-309] (Napolitano et al., *J. Immunol.*, 1996, 157, 2759-2763); CCR-10 (or "CKR-10" or "CC-CKR-10") [MCP-1, MCP-3] (Bonini, et al., *DNA and Cell Biol.* **1997**, 16, 1249-1256); and CCR-11 [MCP-1, MCP-2, and MCP-4] (Schweickert, et al., *J. Biol. Chem.* **2000**, 275, 90550).

In addition to the mammalian chemokine receptors, mammalian cytomegaloviruses, herpesviruses and poxviruses have been shown to express, in infected cells, proteins with the binding properties of chemokine receptors (reviewed in: Wells and Schwartz, *Curr. Opin. Biotech.* **1997**, 8, 741-748). Human CC chemokines, such as RANTES and MCP-3, can cause rapid mobilization of calcium via these virally encoded receptors. Receptor expression may be permissive for infection by allowing for the subversion of normal immune system surveillance and response to infection. Additionally, human chemokine receptors, such as CXCR4, CCR2, CCR3, CCR5 and CCR8, can act as co-receptors for the infection of mammalian cells by microbes as with, for example, the human immunodeficiency viruses (HIV).

The chemokines and their cognate receptors have been implicated as being important mediators of inflammatory,

infectious, and immunoregulatory disorders and diseases, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis (reviewed in: P. H. Carter, *Current Opinion in Chemical Biology* **2002**, 6, 510; Trivedi, et al, *Ann. Reports Med. Chem.* **2000**, 35, 191; Saunders and Tarby, *Drug Disc. Today* **1999**, 4, 80; Premack and Schall, *Nature Medicine* **1996**, 2, 1174). For example, the chemokine monocyte chemoattractant-1 (MCP-1) and its

5 receptor CC Chemokine Receptor 2 (CCR-2) play a pivotal role in attracting leukocytes to sites of inflammation and in subsequently activating these cells. When the chemokine MCP-1 binds to CCR-2, it induces a rapid increase in intracellular calcium concentration,

10 increased expression of cellular adhesion molecules, cellular degranulation, and the promotion of leukocyte migration. Demonstration of the importance of the MCP-1/CCR-2 interaction has been provided by experiments with genetically modified mice. MCP-1 -/- mice had normal

15 numbers of leukocytes and macrophages, but were unable to recruit monocytes into sites of inflammation after several different types of immune challenge (Bao Lu, et al., *J. Exp. Med.* **1998**, 187, 601). Likewise, CCR-2 -/- mice were unable to recruit monocytes or produce

20 interferon- γ when challenged with various exogenous agents; moreover, the leukocytes of CCR-2 null mice did not migrate in response to MCP-1 (Landin Boring, et al., *J. Clin. Invest.* **1997**, 100, 2552), thereby demonstrating the specificity of the MCP-1/CCR-2 interaction. Two

25 other groups have independently reported equivalent results with different strains of CCR-2 -/- mice (William A. Kuziel, et al., *Proc. Natl. Acad. Sci. USA* **1997**, 94, 12053, and Takao Kurihara, et al., *J. Exp. Med.* **1997**,

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186, 1757). The viability and generally normal health of the MCP-1 $-/-$ and CCR-2 $-/-$ animals is noteworthy, in that disruption of the MCP-1/CCR-2 interaction does not induce physiological crisis. Taken together, these data
5 lead one to the conclusion that molecules that block the actions of MCP-1 would be useful in treating a number of inflammatory and autoimmune disorders. This hypothesis has now been validated in a number of different animal disease models, as described below.

10 It is known that MCP-1 is upregulated in patients with rheumatoid arthritis (Alisa Koch, et al., *J. Clin. Invest.* **1992**, *90*, 772 - 779). Moreover, several studies have demonstrated the potential therapeutic value of antagonism of the MCP-1/CCR2 interaction in treating
15 rheumatoid arthritis. A DNA vaccine encoding MCP-1 was shown recently to ameliorate chronic polyadjuvant-induced arthritis in rats (Sawsan Youssef, et al., *J. Clin. Invest.* **2000**, *106*, 361). Likewise, inflammatory disease symptoms could be controlled via direct administration of
20 antibodies for MCP-1 to rats with collagen-induced arthritis (Hiroomi Ogata, et al., *J. Pathol.* **1997**, *182*, 106), or streptococcal cell wall-induced arthritis (Ralph C. Schimmer, et al., *J. Immunol.* **1998**, *160*, 1466). Perhaps most significantly, a peptide antagonist of MCP-
25 1, MCP-1(9-76), was shown both to prevent disease onset and to reduce disease symptoms (depending on the time of administration) in the MRL-lpr mouse model of arthritis (Jiang-Hong Gong, et al., *J. Exp. Med.* **1997**, *186*, 131).

It is known that MCP-1 is upregulated in
30 atherosclerotic lesions, and it has been shown that circulating levels of MCP-1 are reduced through treatment with therapeutic agents, plays a role in disease progression (Abdolreza Rezaie-Majd, et al, *Arterioscler.*

Thromb. Vasc. Biol. **2002**, 22, 1194 - 1199). Four key studies have demonstrated the potential therapeutic value of antagonism of the MCP-1/CCR2 interaction in treating atherosclerosis. For example, when MCP-1 -/- mice are
5 mated with LDL receptor-deficient mice, an 83% reduction in aortic lipid deposition was observed (Long Gu, et al., *Mol. Cell* **1998**, 2, 275). Similarly, when MCP-1 was genetically ablated from mice which already overexpressed human apolipoprotein B, the resulting mice were protected
10 from atherosclerotic lesion formation relative to the MCP-1 +/+ apoB control mice (Jennifa Gosling, et al., *J. Clin. Invest.* **1999**, 103, 773). Likewise, when CCR-2 -/- mice are crossed with apolipoprotein E -/- mice, a significant decrease in the incidence of atherosclerotic
15 lesions was observed (Landin Boring, et al, *Nature* **1998**, 394, 894). Finally, when apolipoprotein E -/- mice are administered a gene encoding a peptide antagonist of CCR2, then lesion size is decreased and plaque stability is increased (W. Ni, et al. *Circulation* **2001**, 103, 2096 -
20 2101).

It is known that MCP-1 is upregulated in human multiple sclerosis, and it has been shown that effective therapy with interferon b-1b reduces MCP-1 expression in peripheral blood mononuclear cells, suggesting that MCP-1
25 plays a role in disease progression (Carla Iarlori, et al., *J. Neuroimmunol.* **2002**, 123, 170 - 179). Other studies have demonstrated the potential therapeutic value of antagonism of the MCP-1/CCR-2 interaction in treating multiple sclerosis; all of these studies have been
30 demonstrated in experimental autoimmune encephalomyelitis (EAE), the conventional animal model for multiple sclerosis. Administration of antibodies for MCP-1 to animals with EAE significantly diminished disease relapse

(K. J. Kennedy, et al., *J. Neuroimmunol.* **1998**, 92, 98).
 Furthermore, two recent reports have now shown that CCR-2
 -/- mice are resistant to EAE (Brian T. Fife, et al., *J.*
Exp. Med. **2000**, 192, 899; Leonid Izikson, et al., *J. Exp.*
 5 *Med.* **2000**, 192, 1075).

It is known that MCP-1 is upregulated in patients
 who develop bronchiolitis obliterans syndrome after lung
 transplantation (Martine Reynaud-Gaubert, et al., *J. of*
Heart and Lung Transplant., **2002**, 21, 721 - 730; John
 10 Belperio, et al., *J. Clin. Invest.* **2001**, 108, 547 - 556).
 In a murine model of bronchiolitis obliterans syndrome,
 administration of an antibody to MCP-1 led to attenuation
 of airway obliteration; likewise, CCR2 -/- mice were
 resistant to airway obliteration in this same model (John
 15 Belperio, et al., *J. Clin. Invest.* **2001**, 108, 547 - 556).
 These data suggest that antagonism of MCP-1/CCR2 may be
 beneficial in treating rejection of organs following
 transplantation.

Other studies have demonstrated the potential
 20 therapeutic value of antagonism of the MCP-1/CCR2
 interaction in treating asthma. Sequestration of MCP-1
 with a neutralizing antibody in ovalbumin-challenged mice
 resulted in marked decrease in bronchial
 hyperresponsiveness and inflammation (Jose-Angel Gonzalo,
 25 et al., *J. Exp. Med.* **1998**, 188, 157). It proved possible
 to reduce allergic airway inflammation in *Schistosoma*
mansoni egg-challenged mice through the administration of
 antibodies for MCP-1 (Nicholas W. Lukacs, et al., *J.*
Immunol. 1997, 158, 4398). Consistent with this, MCP-1
 30 -/- mice displayed a reduced response to challenge with
Schistosoma mansoni egg (Bao Lu, et al., *J. Exp. Med.*
1998, 187, 601).

Other studies have demonstrated the potential therapeutic value of antagonism of the MCP-1/CCR2 interaction in treating kidney disease. Administration of antibodies for MCP-1 in a murine model of
5 glomerular nephritis resulted in a marked decrease in glomerular crescent formation and deposition of type I collagen (Clare M. Lloyd, et al., *J. Exp. Med.* **1997**, *185*, 1371). In addition, MCP-1 -/- mice with induced nephrotoxic serum nephritis showed significantly less
10 tubular damage than their MCP-1 +/+ counterparts (Gregory H. Tesch, et al., *J. Clin. Invest.* **1999**, *103*, 73).

One study has demonstrated the potential therapeutic value of antagonism of the MCP-1/CCR2 interaction in treating systemic lupus erythematosus. Crossing of MCP-1
15 -/- mice with MRL-*FAS*^{lpr} mice -- the latter of which have a fatal autoimmune disease that is analogous to human systemic lupus erythematosus -- results mice that have less disease and longer survival than the wildtype MRL-*FAS*^{lpr} mice (Gregory H. Tesch, et al., *J. Exp. Med.* **1999**,
20 *190*, 1813).

One study has demonstrated the potential therapeutic value of antagonism of the MCP-1/CCR2 interaction in treating colitis. CCR-2 -/- mice were protected from the effects of dextran sodium sulfate-induced colitis (Pietro
25 G. Andres, et al., *J. Immunol.* **2000**, *164*, 6303).

One study has demonstrated the potential therapeutic value of antagonism of the MCP-1/CCR2 interaction in treating alveolitis. When rats with IgA immune complex lung injury were treated intravenously with antibodies
30 raised against rat MCP-1 (JE), the symptoms of alveolitis were partially alleviated (Michael L. Jones, et al., *J. Immunol.* **1992**, *149*, 2147).

One study has demonstrated the potential therapeutic value of antagonism of the MCP-1/CCR2 interaction in treating cancer. When immunodeficient mice bearing human breast carcinoma cells were treated with an anti-MCP-1
5 antibody, inhibition of lung micrometastases and increases in survival were observed (Rosalba Salcedo, et al., *Blood* **2000**, 96, 34 - 40).

One study has demonstrated the potential therapeutic value of antagonism of the MCP-1/CCR2 interaction in
10 treating restinosis. Mice deficient in CCR2 showed reductions in the intimal area and in the intima/media ratio (relative to wildtype littermates) after injury of the femoral artery (Merce Roque, et al. *Arterioscler. Thromb. Vasc. Biol.* **2002**, 22, 554 - 559).

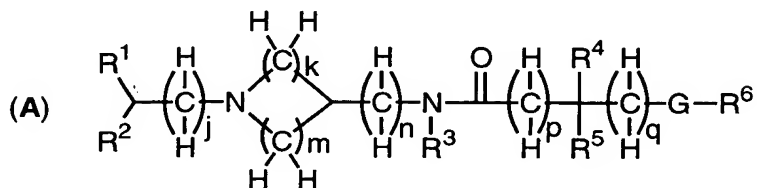
15 Other studies have provided evidence that MCP-1 is overexpressed in various disease states not mentioned above. These reports provide correlative evidence that MCP-1 antagonists could be useful therapeutics for such diseases. Two reports described the overexpression of
20 MCP-1 in the intestinal epithelial cells and bowel mucosa of patients with inflammatory bowel disease (H. C. Reinecker, et al., *Gastroenterology* **1995**, 108, 40, and Michael C. Grimm, et al., *J. Leukoc. Biol.* **1996**, 59, 804). Two reports describe the overexpression of MCP-1
25 rats with induced brain trauma (J. S. King, et al., *J. Neuroimmunol.* **1994**, 56, 127, and Joan W. Berman, et al., *J. Immunol.* **1996**, 156, 3017). Another study has demonstrated the overexpression of MCP-1 in rodent cardiac allografts, suggesting a role for MCP-1 in the
30 pathogenesis of transplant arteriosclerosis (Mary E. Russell, et al. *Proc. Natl. Acad. Sci. USA* **1993**, 90, 6086). The overexpression of MCP-1 has been noted in the lung endothelial cells of patients with idiopathic

pulmonary fibrosis (Harry N. Antoniades, et al., *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 5371). Similarly, the overexpression of MCP-1 has been noted in the skin from patients with psoriasis (M. Deleuran, et al., *J. Dermatol. Sci.* **1996**, *13*, 228, and R. Gillitzer, et al., *J. Invest. Dermatol.* **1993**, *101*, 127). Finally, a recent report has shown that MCP-1 is overexpressed in the brains and cerebrospinal fluid of patients with HIV-1-associated dementia (Alfredo Garzino-Demo, WO 99/46991).

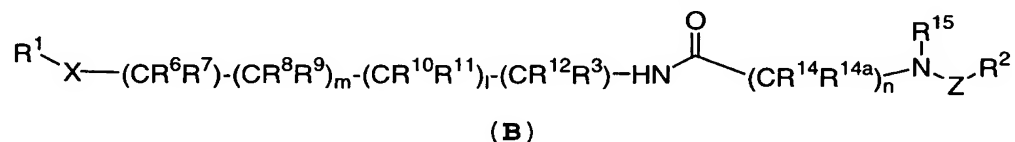
10 It should also be noted that CCR-2 has been implicated as a co-receptor for some strains of HIV (B. J. Doranz, et al., *Cell* **1996**, *85*, 1149). It has also been determined that the use of CCR-2 as an HIV co-receptor can be correlated with disease progression (Ruth I. Connor, et al., *J. Exp. Med.* **1997**, *185*, 621). This finding is consistent with the recent finding that the presence of a CCR-2 mutant, CCR2-64I, is positively correlated with delayed onset of HIV in the human population (Michael W. Smith, et al., *Science* **1997**, *277*, 15 959). Although MCP-1 has not been implicated in these processes, it may be that MCP-1 antagonists that act via binding to CCR-2 may have beneficial therapeutic effects in delaying the disease progression to AIDS in HIV-infected patients.

25 Recently, a number of groups have described the development of small molecule antagonists of MCP-1 (reviewed in: Bharat K. Trivedi, et al, *Ann. Reports Med. Chem.* **2000**, *35*, 191). Workers at Teijen and Combichem reported the use of cyclic amines (**A**) as MCP-1 (Tatsuki Shiota, et al., WO 99/25686; Tatsuki Shiota, et al., WO 30 00/69815) and MIP-1 α (Christine Tarby and Wilna Moree, WO 00/69820) antagonists. These compounds are distinguished

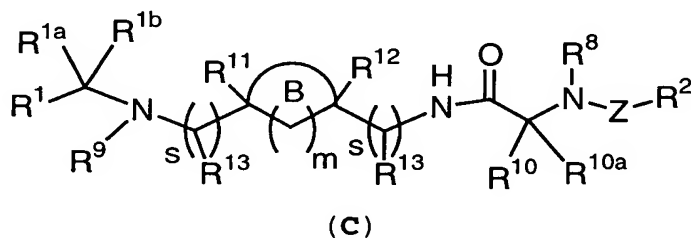
from those of the present invention (I) by the requirement for the central cyclic amine grouping.



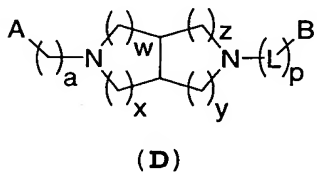
Workers at Bristol-Myers Squibb have reported the use of acyclic diamines (B) as MCP-1 antagonists (Percy Carter and Robert Cherney, WO-02/50019).



Workers at Bristol-Myers Squibb have reported the use of cyclic diamines (C) as MCP-1 antagonists (Robert Cherney, WO-02/060859).



Workers at Pfizer have reported the use of bicyclic diamines (D) as MCP-1 antagonists (Roberto Colon-Cruz, et al., WO-02/070523).



A number of other groups have also described the development of small molecule antagonists of the MCP-1/CCR-2 interaction. To date, indolopiperidines (Ian T. Forbes, et al., *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1803), spiropiperidines (Tara Mirzadegan, et al., *J. Biol. Chem.* **2000**, *275*, 25562), quaternary amines (Masanori Baba, et

al., *Proc. Natl. Acad. Sci.* **1999**, 96, 5698), 2-substituted indoles (Alan Faull and Jason Kettle, WO 00/46196; Andrew John Barker, et al., WO 99/07351; Andrew John Barker, et al., WO 99/07678), pyrazolone derivatives
5 (Janak Khimchand Padia, et al., US patent 6,011,052, 2000), 2-substituted benzimidazoles (David Thomas Connor, et al., WO 98/06703), *N*, *N*-dialkylhomopiperazines (T. Shiota, et al., WO 97/44329), bicyclic pyrroles (Andrew J. Barker, et al., WO 99/40913 and Andrew J. Barker, et
10 al., WO 99/40914), and 5-aryl pentadienamides (K. G. Carson, et al., Cambridge Health Tech Institute Chemokine Symposium, McLean, VA, USA, 1999) have all been reported as MCP-1 antagonists.

The foregoing reference compounds are readily
15 distinguished structurally from the present invention by virtue of substantial differences in the terminal functionality, the attachment functionality, or the core functionality. The prior art does not disclose nor suggest the unique combination of structural fragments
20 that embody in the novel compounds described herein. Furthermore, the prior art does not disclose or suggest that the compounds of the present invention would be antagonists of MCP-1.

It should be noted that CCR-2 is also the receptor
25 for the chemokines MCP-2, MCP-3, MCP-4, and MCP-5 (Luster, *New Eng. J. Med.* **1998**, 338, 436-445). Since the new compounds of formula (I) described herein antagonize MCP-1 by binding to the CCR-2 receptor, it may be that these compounds of formula (I) are also effective
30 antagonists of the actions of MCP-2, MCP-3, MCP-4, and MCP-5 that are mediated by CCR-2. Accordingly, when reference is made herein to "antagonism of MCP-1," it is

to be assumed that this is equivalent to "antagonism of chemokine stimulation of CCR-2."

SUMMARY OF THE INVENTION

5 Accordingly, the present invention provides novel antagonists or partial agonists/antagonists of MCP-1 receptor activity, or pharmaceutically acceptable salts or prodrugs thereof.

10 The present invention provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

15 The present invention provides a method for treating rheumatoid arthritis, multiple sclerosis, and atherosclerosis, comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form
20 thereof.

 The present invention provides a method for treating inflammatory diseases, comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present
25 invention or a pharmaceutically acceptable salt or prodrug form thereof.

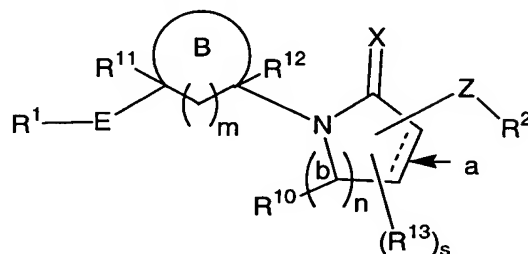
 The present invention provides novel cyclic derivatives for use in therapy.

30 The present invention provides the use of novel cyclic derivatives for the manufacture of a medicament for the treatment of inflammatory diseases.

 The present invention is directed to methods of preparing the compounds of the present invention, and intermediates thereof.

35 These and other features of the invention, which will become apparent during the following detailed

description, have been achieved by the inventors' discovery that compounds of formula (I):



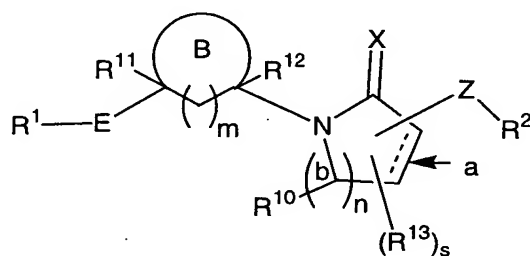
5 (I)

or stereoisomers or pharmaceutically acceptable salts thereof, wherein B, E, Z, m, n, s, carbon b, bond (a), R¹, R², R¹⁰, R¹¹, R¹², and R¹³ are defined below, are
10 effective modulators of chemokine activity.

DETAILED DESCRIPTION OF EMBODIMENTS OF THE PRESENT INVENTION

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[1] Thus, in another embodiment, the present invention provides novel compounds of formula (I):



20

(I)

or a stereoisomer or a pharmaceutically acceptable salt thereof, wherein:

25 ring B is a cycloalkyl group of 3 to 8 carbon atoms wherein the cycloalkyl group is saturated or partially unsaturated; or a heterocycle of 3 to 7

atoms wherein the heterocycle is saturated or partially unsaturated, the heterocycle containing a heteroatom selected from -O-, -S-, -S(=O)-, -S(=O)₂-, and -N(R⁴)-, the heterocycle optionally
 5 containing a -C(O)-; ring B being substituted with 0-2 R⁵;

X is selected from O or S;

10 Z is selected from a bond, -NR⁸C(O)-, -NR⁸C(S)-, -NR⁸C(O)NH-, -NR⁸C(S)NH-, -NR⁸SO₂-, -NR⁸SO₂NH-, -C(O)NR⁸-, -OC(O)NR⁸-, -NR⁸C(O)O-, -(CR¹⁵R¹⁵)₁-, -CR¹⁴=CR¹⁴-, -CR¹⁵R¹⁵C(O)-, -C(O)CR¹⁵R¹⁵-, CR¹⁵R¹⁵C(=N-OR¹⁶)-, -O-CR¹⁴R¹⁴-, -CR¹⁴R¹⁴-O-, -O-,
 15 -NR⁹-, -NR⁹-CR¹⁴R¹⁴-, -CR¹⁴R¹⁴-NR⁹-, -S(O)_p-, -S(O)_p-CR¹⁴R¹⁴-, -CR¹⁴R¹⁴-S(O)_p-, and -S(O)_p-NR⁹;

wherein neither Z nor R¹³ are connected to a carbon atom labeled (b);

20

bond (a) is a single or double bond;

alternatively, when n is equal to 2, two atoms labeled (b) may join through a double bond;

25

E is selected from -S(O)_pCHRe-, -CHReNRe-, -C(O)-NRe-, -NReC(O)NRe-, -SO₂-NRe-, and -NReSO₂NRe-;

Re is independently selected from H and C₁₋₃ alkyl;

30

R¹ is selected from a C₆₋₁₀ aryl group substituted with 0-5 R⁶ and a 5-10 membered heteroaryl system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R⁶;

35

R² is selected from a C₆₋₁₀ aryl group substituted with 0-5 R⁷ and a 5-10 membered heteroaryl system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R⁷;

5

R⁴ is selected from H, C₁₋₆ alkyl, C₃₋₈ alkenyl, C₃₋₈ alkynyl, (CRR)_tOH, (CRR)_tSH, (CRR)_tOR^{4d}, (CHR)_tSR^{4d}, (CRR)_tNR^{4a}R^{4a}, (CRR)_qC(O)OH, (CRR)_rC(O)R^{4b}, (CRR)_rC(O)NR^{4a}R^{4a}, (CRR)_tOC(O)NR^{4a}R^{4a}, (CRR)_tNR^{4a}C(O)OR^{4d}, (CRR)_tNR^{4a}C(O)R^{4b}, (CRR)_rC(O)OR^{4d}, (CRR)_tOC(O)R^{4b}, (CRR)_rS(O)_pR^{4b}, (CRR)_rS(O)₂NR^{4a}R^{4a}, (CRR)_tNR^{4a}S(O)₂R^{4b}, C₁₋₆ haloalkyl, a (CRR)_r-C₃₋₁₀ carbocyclic residue substituted with 0-3 R^{4e}, and a (CHR)_r-4-10 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-2 R^{4e};

15

R^{4a}, at each occurrence, is independently selected from H, methyl substituted with 0-1 R^{4c}, C₂₋₆ alkyl substituted with 0-3 R^{4e}, C₃₋₈ alkenyl substituted with 0-3 R^{4e}, C₃₋₈ alkynyl substituted with 0-3 R^{4e}, a (CH₂)_r-C₃₋₁₀ carbocyclic residue substituted with 0-4 R^{4e}, and a (CHR)_r-4-10 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-2 R^{4e};

20

25

R^{4b}, at each occurrence, is selected from H, C₁₋₆ alkyl substituted with 0-3 R^{4e}, C₃₋₈ alkenyl substituted with 0-3 R^{4e}, C₃₋₈ alkynyl substituted with 0-3 R^{4e}, a (CH₂)_r-C₃₋₆ carbocyclic residue substituted with 0-2 R^{4e}, and a (CHR)_r-4-10 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-2 R^{4e};

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R^{4c} is independently selected from -C(O)R^{4b}, -C(O)OR^{4d},
-C(O)NR^{4f}R^{4f}, and (CH₂)_rphenyl;

5 R^{4d}, at each occurrence, is selected from methyl, CF₃,
C₂₋₆ alkyl substituted with 0-3 R^{4e}, C₃₋₈ alkenyl
substituted with 0-3 R^{4e}, C₃₋₈ alkynyl substituted
with 0-3 R^{4e}, and a C₃₋₁₀ carbocyclic residue
substituted with 0-3 R^{4e};

10 R^{4e}, at each occurrence, is selected from C₁₋₆ alkyl, C₂₋₈
alkenyl, C₂₋₈ alkynyl, (CH₂)_rC₃₋₆ cycloalkyl, Cl, F,
Br, I, CN, NO₂, (CF₂)_rCF₃, (CH₂)_rOC₁₋₅ alkyl, OH, SH,
(CH₂)_rSC₁₋₅ alkyl, (CH₂)_rNR^{4f}R^{4f}, -C(O)R⁴ⁱ, -C(O)OR^{4j},
-C(O)NR^{4h}R^{4h}, -OC(O)NR^{4h}R^{4h}, -NR^{4h}C(O)NR^{4h}R^{4h},
15 -NR^{4h}C(O)OR^{4j}, and (CH₂)_rphenyl;

R^{4f}, at each occurrence, is selected from H, C₁₋₆ alkyl,
C₃₋₆ cycloalkyl, and phenyl;

20 R^{4h}, at each occurrence, is independently selected from H,
C₁₋₆ alkyl, C₃₋₈ alkenyl, C₃₋₈ alkynyl, and a
(CH₂)_r-C₃₋₁₀ carbocyclic;

25 R⁴ⁱ, at each occurrence, is selected from H, C₁₋₆ alkyl,
C₃₋₈ alkenyl, C₃₋₈ alkynyl, and a (CH₂)_r-C₃₋₆
carbocyclic residue;

30 R^{4j}, at each occurrence, is selected from CF₃, C₁₋₆ alkyl,
C₃₋₈ alkenyl, C₃₋₈ alkynyl, and a C₃₋₁₀ carbocyclic
residue;

R⁵, at each occurrence, is independently selected from H,
=O, C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, (CRR)_rOH,
(CRR)_rSH, (CRR)_rOR^{5d}, (CRR)_rSR^{5d}, (CRR)_rNR^{5a}R^{5a},

$(\text{CRR})_r\text{N}(\rightarrow\text{O})\text{R}^{5a}\text{R}^{5a}$, N_3 , $(\text{CRR})_r\text{C}(\text{O})\text{OH}$, $(\text{CRR})_r\text{C}(\text{O})\text{R}^{5b}$,
 $(\text{CRR})_r\text{C}(\text{O})\text{NR}^{5a}\text{R}^{5a}$, $(\text{CRR})_r\text{NR}^{5a}\text{C}(\text{O})\text{R}^{5b}$,
 $(\text{CRR})_r\text{OC}(\text{O})\text{NR}^{5a}\text{R}^{5a}$, $(\text{CRR})_r\text{NR}^{5a}\text{C}(\text{O})\text{OR}^{5d}$,
 $(\text{CRR})_r\text{NR}^{5a}\text{C}(\text{O})\text{NR}^{5a}\text{R}^{5a}$, $(\text{CRR})_r\text{NR}^{5a}\text{C}(\text{O})\text{H}$,
5 $(\text{CRR})_r\text{C}(\text{O})\text{OR}^{5d}$, $(\text{CRR})_r\text{OC}(\text{O})\text{R}^{5b}$, $(\text{CRR})_r\text{S}(\text{O})_p\text{R}^{5b}$,
 $(\text{CRR})_r\text{S}(\text{O})_2\text{NR}^{5a}\text{R}^{5a}$, $(\text{CRR})_r\text{NR}^{5a}\text{S}(\text{O})_2\text{R}^{5b}$,
 $(\text{CRR})_r\text{NR}^{5a}\text{S}(\text{O})_2\text{NR}^{5a}\text{R}^{5a}$, C_{1-6} haloalkyl, a $(\text{CRR})_r\text{-C}_{3-10}$
carbocyclic residue substituted with 0-3 R^{5c} , and a
 $(\text{CRR})_r\text{-5-10}$ membered heterocyclic system containing
10 1-4 heteroatoms selected from N, O, and S,
substituted with 0-2 R^{5c} ;

R^{5a} , at each occurrence, is independently selected from H,
methyl substituted with 0-1 R^{5g} , C_{2-6} alkyl
15 substituted with 0-2 R^{5e} , C_{3-8} alkenyl substituted
with 0-2 R^{5e} , C_{3-8} alkynyl substituted with 0-2 R^{5e} ,
a $(\text{CH}_2)_r\text{-C}_{3-10}$ carbocyclic residue substituted with
0-5 R^{5e} , and a $(\text{CH}_2)_r\text{-5-10}$ membered heterocyclic
system containing 1-4 heteroatoms selected from N,
20 O, and S, substituted with 0-3 R^{5e} ;

R^{5b} , at each occurrence, is selected from C_{1-6} alkyl
substituted with 0-3 R^{5e} , C_{3-8} alkenyl substituted
with 0-2 R^{5e} , C_{3-8} alkynyl substituted with 0-2 R^{5e} ,
25 a $(\text{CH}_2)_r\text{-C}_{3-6}$ carbocyclic residue substituted with
0-2 R^{5e} , and a $(\text{CH}_2)_r\text{-5-6}$ membered heterocyclic
system containing 1-4 heteroatoms selected from N,
O, and S, substituted with 0-3 R^{5e} ;

30 R^{5c} , at each occurrence, is selected from C_{1-6} alkyl, C_{2-8}
alkenyl, C_{2-8} alkynyl, $(\text{CH}_2)_r\text{C}_{3-6}$ cycloalkyl, Cl, Br,
I, F, $(\text{CF}_2)_r\text{CF}_3$, NO_2 , CN, $(\text{CH}_2)_r\text{NR}^{5f}\text{R}^{5f}$, $(\text{CH}_2)_r\text{OH}$,
 $(\text{CH}_2)_r\text{OC}_{1-4}$ alkyl, $(\text{CH}_2)_r\text{SC}_{1-4}$ alkyl, $(\text{CH}_2)_r\text{C}(\text{O})\text{OH}$,

$(\text{CH}_2)_r\text{C}(\text{O})\text{R}^{5b}$, $(\text{CH}_2)_r\text{C}(\text{O})\text{NR}^{5f}\text{R}^{5f}$, $(\text{CH}_2)_r\text{OC}(\text{O})\text{NR}^{5f}\text{R}^{5f}$,
 $(\text{CH}_2)_r\text{NR}^{5f}\text{C}(\text{O})\text{R}^{5b}$, $(\text{CH}_2)_r\text{C}(\text{O})\text{OC}_{1-4}\text{ alkyl}$,
 $(\text{CH}_2)_r\text{NR}^{5f}\text{C}(\text{O})\text{OC}_{1-4}\text{ alkyl}$, $(\text{CH}_2)_r\text{OC}(\text{O})\text{R}^{5b}$,
 $(\text{CH}_2)_r\text{C}(=\text{NR}^{5f})\text{NR}^{5f}\text{R}^{5f}$, $(\text{CH}_2)_r\text{S}(\text{O})_p\text{R}^{5b}$,
5 $(\text{CH}_2)_r\text{NHC}(=\text{NR}^{5f})\text{NR}^{5f}\text{R}^{5f}$, $(\text{CH}_2)_r\text{S}(\text{O})_2\text{NR}^{5f}\text{R}^{5f}$,
 $(\text{CH}_2)_r\text{NR}^{5f}\text{S}(\text{O})_2\text{R}^{5b}$, and $(\text{CH}_2)_r\text{phenyl}$ substituted with
0-3 R^{5e} ;

10 R^{5d} , at each occurrence, is selected from methyl, CF_3 ,
 C_{2-6} alkyl substituted with 0-2 R^{5e} , C_{3-8} alkenyl
substituted with 0-2 R^{5e} , C_{3-8} alkynyl substituted
with 0-2 R^{5e} , and a C_{3-10} carbocyclic residue
substituted with 0-3 R^{5e} ;

15 R^{5e} , at each occurrence, is selected from C_{1-6} alkyl, C_{2-8}
alkenyl, C_{2-8} alkynyl, C_{3-6} cycloalkyl, Cl, F, Br, I,
CN, NO_2 , $(\text{CF}_2)_r\text{CF}_3$, $(\text{CH}_2)_r\text{OC}_{1-5}\text{ alkyl}$, OH, SH,
 $(\text{CH}_2)_r\text{SC}_{1-5}\text{ alkyl}$, $(\text{CH}_2)_r\text{NR}^{5f}\text{R}^{5f}$, and $(\text{CH}_2)_r\text{phenyl}$;

20 R^{5f} , at each occurrence, is selected from H, C_{1-6} alkyl,
and C_{3-6} cycloalkyl;

R^{5g} is independently selected from $-\text{C}(\text{O})\text{R}^{5b}$, $-\text{C}(\text{O})\text{OR}^{5d}$,
 $-\text{C}(\text{O})\text{NR}^{5f}\text{R}^{5f}$, $-\text{CN}$, and $(\text{CH}_2)_r\text{phenyl}$;

25 R , at each occurrence, is selected from H, C_{1-6} alkyl
substituted with R^{5e} , C_{2-8} alkenyl, C_{2-8} alkynyl,
 $(\text{CH}_2)_r\text{C}_{3-6}$ cycloalkyl, and $(\text{CH}_2)_r\text{phenyl}$ substituted
with R^{5e} ;

30 R^6 , at each occurrence, is selected from C_{1-8} alkyl, C_{2-8}
alkenyl, C_{2-8} alkynyl, $(\text{CH}_2)_r\text{C}_{3-6}$ cycloalkyl, Cl, Br,
I, F, NO_2 , CN, $(\text{CR}'\text{R}')_r\text{NR}^{6a}\text{R}^{6a}$, $(\text{CR}'\text{R}')_r\text{OH}$,

- $(\text{CR}'\text{R}')_r\text{O}(\text{CR}'\text{R}')_r\text{R}^{6d}$, $(\text{CR}'\text{R}')_r\text{SH}$, $(\text{CR}'\text{R}')_r\text{C}(\text{O})\text{H}$,
 $(\text{CR}'\text{R}')_r\text{S}(\text{CR}'\text{R}')_r\text{R}^{6d}$, $(\text{CR}'\text{R}')_r\text{SC}(\text{O})(\text{CR}'\text{R}')_r\text{R}^{6b}$,
 $(\text{CR}'\text{R}')_r\text{C}(\text{O})\text{OH}$, $(\text{CR}'\text{R}')_r\text{C}(\text{O})(\text{CR}'\text{R}')_r\text{R}^{6b}$,
 $(\text{CR}'\text{R}')_r\text{NR}^{6a}\text{R}^{6a}$, $(\text{CR}'\text{R}')_r\text{C}(\text{O})\text{NR}^{6a}\text{R}^{6a}$,
5 $(\text{CR}'\text{R}')_r\text{NR}^{6f}\text{C}(\text{O})(\text{CR}'\text{R}')_r\text{R}^{6b}$, $(\text{CR}'\text{R}')_r\text{C}(\text{O})\text{O}(\text{CR}'\text{R}')_r\text{R}^{6d}$,
 $(\text{CR}'\text{R}')_r\text{OC}(\text{O})(\text{CR}'\text{R}')_r\text{R}^{6b}$,
 $(\text{CR}'\text{R}')_r\text{OC}(\text{O})\text{NR}^{6a}(\text{CR}'\text{R}')_r\text{R}^{6d}$,
 $(\text{CR}'\text{R}')_r\text{NR}^{6a}\text{C}(\text{O})\text{NR}^{6a}(\text{CR}'\text{R}')_r\text{R}^{6d}$,
 $(\text{CR}'\text{R}')_r\text{NR}^{6a}\text{C}(\text{S})\text{NR}^{6a}(\text{CR}'\text{R}')_r\text{R}^{6d}$,
10 $(\text{CR}'\text{R}')_r\text{NR}^{6f}\text{C}(\text{O})\text{O}(\text{CR}'\text{R}')_r\text{R}^{6b}$, $(\text{CR}'\text{R}')_r\text{C}(=\text{NR}^{6f})\text{NR}^{6a}\text{R}^{6a}$,
 $(\text{CR}'\text{R}')_r\text{NHC}(=\text{NR}^{6f})\text{NR}^{6f}\text{R}^{6f}$, $(\text{CR}'\text{R}')_r\text{S}(\text{O})_p(\text{CR}'\text{R}')_r\text{R}^{6b}$,
 $(\text{CR}'\text{R}')_r\text{S}(\text{O})_2\text{NR}^{6a}\text{R}^{6a}$, $(\text{CR}'\text{R}')_r\text{NR}^{6f}\text{S}(\text{O})_2\text{NR}^{6a}\text{R}^{6a}$,
 $(\text{CR}'\text{R}')_r\text{NR}^{6f}\text{S}(\text{O})_2(\text{CR}'\text{R}')_r\text{R}^{6b}$, C_{1-6} haloalkyl, C_{2-8}
alkenyl substituted with 0-3 R' , C_{2-8} alkynyl
15 substituted with 0-3 R' , $(\text{CR}'\text{R}')_r$ phenyl substituted
with 0-3 R^{6e} , and a $(\text{CH}_2)_r$ -5-6 membered heterocyclic
system containing 1-2 heteroatoms selected from N,
O, and S, substituted with 0-2 R^{6e} ;
20 alternatively, two R^6 on adjacent atoms on R^1 may join to
form a cyclic acetal;

- R^{6a} , at each occurrence, is selected from H, methyl
substituted with 0-1 R^{6g} , C_{2-6} alkyl substituted with
25 0-2 R^{6e} , C_{3-8} alkenyl substituted with 0-2 R^{6e} , C_{3-8}
alkynyl substituted with 0-2 R^{6e} , a $(\text{CH}_2)_r$ - C_{3-10}
carbocyclic residue substituted with 0-5 R^{6e} , and a
 $(\text{CH}_2)_r$ -5-10 membered heterocyclic system containing
1-4 heteroatoms selected from N, O, and S,
30 substituted with 0-2 R^{6e} ;

R^{6b} , at each occurrence, is selected from H, C_{1-6} alkyl
substituted with 0-2 R^{6e} , C_{3-8} alkenyl substituted

with 0-2 R^{6e}, C₃₋₈ alkynyl substituted with 0-2 R^{6e},
 a (CH₂)_rC₃₋₆ carbocyclic residue substituted with 0-3
 R^{6e}, and a (CH₂)_r-5-6 membered heterocyclic system
 containing 1-4 heteroatoms selected from N, O, and
 5 S, substituted with 0-2 R^{6e};

R^{6d}, at each occurrence, is selected from C₃₋₈ alkenyl
 substituted with 0-2 R^{6e}, C₃₋₈ alkynyl substituted
 with 0-2 R^{6e}, methyl, CF₃, C₂₋₆ alkyl substituted
 10 with 0-3 R^{6e}, C₂₋₄ haloalkyl, a (CH₂)_r-C₃₋₁₀
 carbocyclic residue substituted with 0-3 R^{6e}, and a
 (CH₂)_r-5-6 membered heterocyclic system containing
 1-4 heteroatoms selected from N, O, and S,
 substituted with 0-3 R^{6e};

15 R^{6e}, at each occurrence, is selected from C₁₋₆ alkyl, C₂₋₈
 alkenyl, C₂₋₈ alkynyl, (CH₂)_rC₃₋₆ cycloalkyl, Cl, F,
 Br, I, CN, NO₂, (CF₂)_rCF₃, (CH₂)_rOC₁₋₅ alkyl, OH, SH,
 (CH₂)_rSC₁₋₅ alkyl, (CH₂)_rNR^{6f}R^{6f}, and (CH₂)_rphenyl;

20 R^{6f}, at each occurrence, is selected from H, C₁₋₅ alkyl,
 and C₃₋₆ cycloalkyl, and phenyl;

R^{6g} is independently selected from -C(O)R^{6b}, -C(O)OR^{6d},
 25 -C(O)NR^{6f}R^{6f}, and (CH₂)_rphenyl;

R⁷, at each occurrence, is selected from C₁₋₈ alkyl, C₂₋₈
 alkenyl, C₂₋₈ alkynyl, (CH₂)_rC₃₋₆ cycloalkyl, Cl, Br,
 I, F, NO₂, CN, (CR'R')_rNR^{7a}R^{7a}, (CR'R')_rOH,
 30 (CR'R')_rO(CR'R')_rR^{7d}, (CR'R')_rSH, (CR'R')_rC(O)H,
 (CR'R')_rS(CR'R')_rR^{7d}, (CR'R')_rC(O)OH,
 (CR'R')_rC(O)(CR'R')_rR^{7b}, (CR'R')_rC(O)NR^{7a}R^{7a},
 (CR'R')_rNR^{7f}C(O)(CR'R')_rR^{7b}, (CR'R')_rC(O)O(CR'R')_rR^{7d},
 (CR'R')_rOC(O)(CR'R')_rR^{7b},

$(CR'R')_r OC(O)NR^{7a}(CR'R')_r R^{7a}$,
 $(CR'R')_r NR^{7a}C(O)NR^{7a}(CR'R')_r R^{7a}$,
 $(CR'R')_r NR^{7f}C(O)O(CR'R')_r R^{7d}$, $(CR'R')_r C(=NR^{7f})NR^{7a}R^{7a}$,
 $(CR'R')_r NHC(=NR^{7f})NR^{7f}R^{7f}$, $(CR'R')_r S(O)_p(CR'R')_r R^{7b}$,
5 $(CR'R')_r S(O)_2NR^{7a}R^{7a}$, $(CR'R')_r NR^{7a}S(O)_2NR^{7a}R^{7a}$,
 $(CR'R')_r NR^{7f}S(O)_2(CR'R')_r R^{7b}$, C_{1-6} haloalkyl, C_{2-8}
alkenyl substituted with 0-3 R' , C_{2-8} alkynyl
substituted with 0-3 R' , $(CR'R')_r C_{3-10}$ carbocyclic
residue and $(CR'R')_r$ phenyl substituted with 0-3 R^{7e} ;
10 alternatively, two R^7 on adjacent atoms on R^2 may join to
form a cyclic acetal;

R^{7a} , at each occurrence, is independently selected from H,
15 methyl substituted with 0-1 R^{7g} , C_{2-6} alkyl
substituted with 0-2 R^{7e} , C_{3-8} alkenyl substituted
with 0-2 R^{7e} , C_{3-8} alkynyl substituted with 0-2 R^{7e} ,
a $(CH_2)_r$ - C_{3-10} carbocyclic residue substituted with
0-5 R^{7e} , and a $(CH_2)_r$ -5-10 membered heterocyclic
20 system containing 1-4 heteroatoms selected from N,
O, and S, substituted with 0-2 R^{7e} ;

R^{7b} , at each occurrence, is selected from C_{1-6} alkyl
substituted with 0-2 R^{7e} , C_{3-8} alkenyl substituted
25 with 0-2 R^{7e} , C_{3-8} alkynyl substituted with 0-2 R^{7e} ,
a $(CH_2)_r$ - C_{3-6} carbocyclic residue substituted with 0-3
 R^{7e} , and a $(CH_2)_r$ -5-6 membered heterocyclic system
containing 1-4 heteroatoms selected from N, O, and
S, substituted with 0-2 R^{7e} ;
30

R^{7d} , at each occurrence, is selected from C_{3-8} alkenyl
substituted with 0-2 R^{7e} , C_{3-8} alkynyl substituted
with 0-2 R^{7e} , methyl, CF_3 , C_{2-4} haloalkyl, C_{2-6} alkyl

substituted with 0-3 R^{7e} , a $(CH_2)_r$ -C₃₋₁₀ carbocyclic
 residue substituted with 0-3 R^{7e} , and a $(CH_2)_r$ -5-6
 membered heterocyclic system containing 1-4
 heteroatoms selected from N, O, and S, substituted
 5 with 0-3 R^{7e} ;

R^{7e} , at each occurrence, is selected from C₁₋₆ alkyl, C₂₋₈
 alkenyl, C₂₋₈ alkynyl, $(CH_2)_r$ C₃₋₆ cycloalkyl, Cl, F,
 Br, I, CN, NO₂, $(CF_2)_r$ CF₃, $(CH_2)_r$ OC₁₋₅ alkyl, OH, SH,
 10 C(O)OC₁₋₅ alkyl, $(CH_2)_r$ SC₁₋₅ alkyl, $(CH_2)_r$ NR^{7f}R^{7f}, and
 $(CH_2)_r$ phenyl;

R^{7f} , at each occurrence, is selected from H, C₁₋₅ alkyl,
 and C₃₋₆ cycloalkyl, and phenyl;

15 R^{7g} is independently selected from -C(O) R^{7b} , -C(O)OR^{7d},
 -C(O)NR^{7f}R^{7f}, and $(CH_2)_r$ phenyl;

R' , at each occurrence, is selected from H, C₁₋₆ alkyl
 20 substituted with R^{6e} , C₂₋₈ alkenyl, C₂₋₈ alkynyl,
 $(CH_2)_r$ C₃₋₆ cycloalkyl, and $(CH_2)_r$ phenyl substituted
 with R^{6e} ;

R^8 is selected from H, C₁₋₄ alkyl, and C₃₋₄ cycloalkyl;

25 R^9 is selected from H, C₁₋₄ alkyl, C₃₋₄ cycloalkyl,
 -C(O)H, and -C(O)-C₁₋₄alkyl;

R^{10} is independently selected from H, and C₁₋₄alkyl
 30 substituted with 0-1 R^{10b} , alternatively, two R^{10}
 form =O;

R^{10b} , at each occurrence, is independently selected from
 -OH, -SH, -NR^{10c}R^{10c}, -C(O)NR^{10c}R^{10c}, and -NHC(O)R^{10c};

R^{10c} is selected from H, C_{1-4} alkyl and C_{3-6} cycloalkyl;

R^{11} is selected from H, C_{1-4} alkyl, $(CHR)_qOH$, $(CHR)_qSH$,
 5 $(CHR)_qOR^{11d}$, $(CHR)_qS(O)_pR^{11d}$, $(CHR)_rC(O)R^{11b}$,
 $(CHR)_rNR^{11a}R^{11a}$, $(CHR)_rC(O)NR^{11a}R^{11a}$,
 $(CHR)_rC(O)NR^{11a}OR^{11d}$, $(CHR)_qNR^{11a}C(O)R^{11b}$,
 $(CHR)_qNR^{11a}C(O)OR^{11d}$, $(CHR)_qOC(O)NR^{11a}R^{11a}$,
 $(CHR)_rC(O)OR^{11d}$, a $(CHR)_r-C_{3-6}$ carbocyclic residue
 10 substituted with 0-5 R^{11e} , and a $(CHR)_r-5-10$ membered
 heterocyclic system containing 1-4 heteroatoms
 selected from N, O, and S, substituted with 0-3 R^{11e} ;

R^{11a} , at each occurrence, is independently selected from
 15 H, C_{1-4} alkyl, C_{3-4} alkenyl, C_{3-4} alkynyl, $(CH_2)_rC_{3-6}$
 cycloalkyl, a $(CH_2)_r-C_{3-6}$ carbocyclic residue
 substituted with 0-5 R^{11e} , and a $(CH_2)_r-5-6$ membered
 heterocyclic system containing 1-4 heteroatoms
 selected from N, O, and S, substituted with 0-3 R^{11e} ;

20 R^{11b} , at each occurrence, is independently selected from
 C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, a $(CH_2)_r-C_{3-6}$
 carbocyclic residue substituted with 0-2 R^{11e} , and a
 $(CH_2)_r-5-6$ membered heterocyclic system containing
 25 1-4 heteroatoms selected from N, O, and S,
 substituted with 0-3 R^{11e} ;

R^{11d} , at each occurrence, is independently selected from
 H, methyl, $-CF_3$, C_{2-4} alkyl, C_{3-6} alkenyl, C_{3-6}
 30 alkynyl, a C_{3-6} carbocyclic residue substituted with
 0-3 R^{11e} , and a $(CH_2)_r-5-6$ membered heterocyclic

system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{11e};

R^{11e}, at each occurrence, is selected from C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₆ cycloalkyl, Cl, F, Br, I, CN, NO₂, (CF₂)_rCF₃, (CH₂)_rOC₁₋₅ alkyl, OH, -O-C₁₋₆ alkyl, SH, (CH₂)_rSC₁₋₅ alkyl, (CH₂)_rNR^{11f}R^{11f}, and (CH₂)_rphenyl;

R^{11f}, at each occurrence, is selected from H, C₁₋₆ alkyl, and C₃₋₆ cycloalkyl;

R¹² is selected from H, C₁₋₄ alkyl, (CHR)_qOH, (CHR)_qSH, (CHR)_qOR^{12d}, (CHR)_qS(O)_pR^{12d}, (CHR)_rC(O)R^{12b}, (CHR)_rNR^{12a}R^{12a}, (CHR)_rC(O)NR^{12a}R^{12a}, (CHR)_rC(O)NR^{12a}OR^{12d}, (CHR)_qNR^{12a}C(O)R^{12b}, (CHR)_qNR^{12a}C(O)OR^{12d}, (CHR)_qOC(O)NR^{12a}R^{12a}, (CHR)_rC(O)OR^{12d}, a (CHR)_r-C₃₋₆ carbocyclic residue substituted with 0-5 R^{12e}, and a (CHR)_r-5-10 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{12e};

R^{12a}, at each occurrence, is independently selected from H, C₁₋₄ alkyl, C₃₋₄ alkenyl, C₃₋₄ alkynyl, (CH₂)_rC₃₋₆ cycloalkyl, a (CH₂)_r-C₃₋₆ carbocyclic residue substituted with 0-5 R^{12e}, and a (CH₂)_r-5-6 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{12e};

R^{12b}, at each occurrence, is independently selected from C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, a (CH₂)_r-C₃₋₆

carbocyclic residue substituted with 0-2 R^{12e} , and a
 $(CH_2)_r$ -5-6 membered heterocyclic system containing
 1-4 heteroatoms selected from N, O, and S,
 substituted with 0-3 R^{12e} ;

5

R^{12d} , at each occurrence, is independently selected from
 H, methyl, $-CF_3$, C_{2-4} alkyl, C_{3-6} alkenyl, C_{3-6}
 alkynyl, a C_{3-6} carbocyclic residue substituted with
 0-3 R^{12e} , and a $(CH_2)_r$ -5-6 membered heterocyclic
 10 system containing 1-4 heteroatoms selected from N,
 O, and S, substituted with 0-3 R^{12e} ;

R^{12e} , at each occurrence, is selected from C_{1-6} alkyl, C_{2-8}
 alkenyl, C_{2-8} alkynyl, C_{3-6} cycloalkyl, Cl, F, Br, I,
 15 CN, NO_2 , $(CF_2)_rCF_3$, $(CH_2)_rOC_{1-5}$ alkyl, OH, $-O-C_{1-6}$
 alkyl, SH, $(CH_2)_rSC_{1-5}$ alkyl, $(CH_2)_rNR^{12f}R^{12f}$, and
 $(CH_2)_r$ phenyl;

R^{12f} , at each occurrence, is selected from H, C_{1-6} alkyl,
 20 and C_{3-6} cycloalkyl;

R^{13} , at each occurrence, is independently selected from H,
 and C_{1-4} alkyl substituted with 0-1 R^{13b} , $-OH$, $-NH_2$,
 F, Cl, Br, I, $-OR^{13a}$, $-N(R^{13a})_2$, and C_{1-4} alkyl
 25 substituted with 0-3 R^{13b} ;

R^{13a} is selected from H, C_{1-4} alkyl and C_{3-6} cycloalkyl;

R^{13b} , at each occurrence, is independently selected from
 30 $-OH$, $-SH$, $-NR^{13c}R^{13c}$, $-C(O)NR^{13c}R^{13c}$, and $-NHC(O)R^{13c}$;

R^{13c} is selected from H, C_{1-4} alkyl and C_{3-6} cycloalkyl;

R¹⁴, at each occurrence, is independently selected from H and C₁₋₄alkyl;

5 alternatively, two R¹⁴s, along with the carbon atom to which they are attached, join to form a C₃₋₆ carbocyclic ring;

R¹⁵, at each occurrence, is independently selected from H,
 10 C₁₋₄alkyl, OH, NH₂, -O-C₁₋₄ alkyl, NR^{15a}R^{15a},
 C(O)NR^{15a}R^{15a}, NR^{15a}C(O)R^{15b}, NR^{15a}C(O)OR^{15d},
 OC(O)NR^{15a}R^{15a}, and (CHR)_xC(O)OR^{15d};

alternatively, two R¹⁵s, along with the carbon atom or
 15 atoms to which they are attached, join to form a C₃₋₆ carbocyclic ring;

R^{15a}, at each occurrence, is independently selected from H, and C₁₋₄ alkyl;

20 R^{15b}, at each occurrence, is independently selected from C₁₋₄ alkyl, C₃₋₆ alkenyl, and C₃₋₆ alkynyl;

R^{15d}, at each occurrence, is independently selected from
 25 C₁₋₄ alkyl, C₃₋₆ alkenyl, and C₃₋₆ alkynyl;

R¹⁶ is selected from C₁₋₄ alkyl;

l is selected from 1, 2 and 3;

30 n is selected from 0, 1, 2, and 3;

m is selected from 0 and 1;

p, at each occurrence, is independently selected from 0, 1, and 2;

5

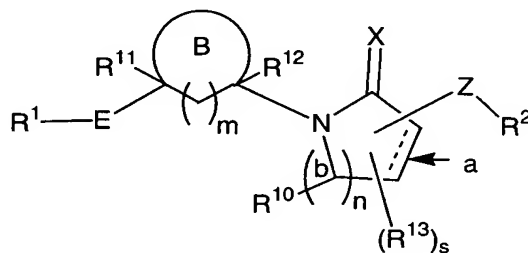
q, at each occurrence, is independently selected from 1, 2, 3, and 4;

10 r, at each occurrence, is independently selected from 0,
 1, 2, 3, and 4;

t, at each occurrence, is independently selected from 2, 3, and 4;

15 s is selected from 0 and 1.

[2] Thus, in another embodiment, the present invention provides novel compounds of formula (I):



20

(I)

or a stereoisomer or a pharmaceutically acceptable salt thereof, wherein:

ring B is a cycloalkyl group of 3 to 8 carbon atoms wherein the cycloalkyl group is saturated or partially unsaturated; or a heterocycle of 3 to 7 atoms wherein the heterocycle is saturated or partially unsaturated, the heterocycle containing a heteroatom selected from -O-, -S-, -S(=O)-, -S(=O)₂-, and -N(R⁴)-, the heterocycle optionally containing a -C(O)-; ring B being substituted with 0-2 R⁵;

X is selected from O or S;

Z is selected from a bond, $\text{-NR}^8\text{C(O)-}$, $\text{-NR}^8\text{C(S)-}$,
 5 $\text{-NR}^8\text{C(O)NH-}$, $\text{-NR}^8\text{C(S)NH-}$, $\text{-NR}^8\text{SO}_2\text{-}$, $\text{-NR}^8\text{SO}_2\text{NH-}$,
 $\text{-C(O)NR}^8\text{-}$, $\text{-OC(O)NR}^8\text{-}$, $\text{-NR}^8\text{C(O)O-}$, $\text{-(CR}^{15}\text{R}^{15})_1\text{-}$,
 $\text{-CR}^{14}=\text{CR}^{14}\text{-}$, $\text{-CR}^{15}\text{R}^{15}\text{C(O)-}$, $\text{-C(O)CR}^{15}\text{R}^{15}\text{-}$,
 $\text{CR}^{15}\text{R}^{15}\text{C(=N-OR}^{16})\text{-}$, $\text{-O-CR}^{14}\text{R}^{14}\text{-}$, $\text{-CR}^{14}\text{R}^{14}\text{-O-}$, -O- ,
 $\text{-NR}^9\text{-}$, $\text{-NR}^9\text{-CR}^{14}\text{R}^{14}\text{-}$, $\text{-CR}^{14}\text{R}^{14}\text{-NR}^9\text{-}$, $\text{-S(O)}_p\text{-}$, $\text{-S(O)}_p\text{-}$
 10 $\text{CR}^{14}\text{R}^{14}\text{-}$, $\text{-CR}^{14}\text{R}^{14}\text{-S(O)}_p\text{-}$, and $\text{-S(O)}_p\text{-NR}^9\text{-}$;

wherein neither Z nor R^{13} are connected to a carbon atom labeled (b);

15 bond (a) is a single or double bond;

alternatively, when n is equal to 2, two atoms labeled (b) may join through a double bond;

20 E is selected from $\text{-S(O)}_p\text{CHRE-}$, $\text{-CHRE}^e\text{NRE-}$, -C(O)-NRE- ,
 $\text{-NRE}^e\text{C(O)NRE-}$, $\text{-SO}_2\text{-NRE-}$, and $\text{-NRE}^e\text{SO}_2\text{NRE-}$;

R^e is independently selected from H and C_{1-3} alkyl;

25 R^1 is selected from a C_{6-10} aryl group substituted with
 0-5 R^6 and a 5-10 membered heteroaryl system
 containing 1-4 heteroatoms selected from N, O, and
 S, substituted with 0-3 R^6 ;

30 R^2 is selected from a C_{6-10} aryl group substituted with
 0-5 R^7 and a 5-10 membered heteroaryl system
 containing 1-4 heteroatoms selected from N, O, and
 S, substituted with 0-3 R^7 ;

R^4 is selected from H, C_{1-6} alkyl, C_{3-8} alkenyl, C_{3-8} alkynyl, $(CRR)_tOH$, $(CRR)_tSH$, $(CRR)_tOR^{4d}$, $(CHR)_tSR^{4d}$, $(CRR)_tNR^{4a}R^{4a}$, $(CRR)_qC(O)OH$, $(CRR)_rC(O)R^{4b}$, $(CRR)_rC(O)NR^{4a}R^{4a}$, $(CRR)_tOC(O)NR^{4a}R^{4a}$,
 5 $(CRR)_tNR^{4a}C(O)OR^{4d}$, $(CRR)_tNR^{4a}C(O)R^{4b}$, $(CRR)_rC(O)OR^{4d}$, $(CRR)_tOC(O)R^{4b}$, $(CRR)_rS(O)_pR^{4b}$, $(CRR)_rS(O)_2NR^{4a}R^{4a}$, $(CRR)_tNR^{4a}S(O)_2R^{4b}$, C_{1-6} haloalkyl, a $(CRR)_r-C_{3-10}$ carbocyclic residue substituted with 0-3 R^{4e} , and a $(CHR)_r-4-10$ membered heterocyclic system containing
 10 1-4 heteroatoms selected from N, O, and S, substituted with 0-2 R^{4e} ;

R^{4a} , at each occurrence, is independently selected from H, methyl substituted with 0-1 R^{4c} , C_{2-6} alkyl
 15 substituted with 0-3 R^{4e} , C_{3-8} alkenyl substituted with 0-3 R^{4e} , C_{3-8} alkynyl substituted with 0-3 R^{4e} , a $(CH_2)_r-C_{3-10}$ carbocyclic residue substituted with 0-4 R^{4e} , and a $(CHR)_r-4-10$ membered heterocyclic system containing 1-4 heteroatoms selected from N,
 20 O, and S, substituted with 0-2 R^{4e} ;

R^{4b} , at each occurrence, is selected from H, C_{1-6} alkyl substituted with 0-3 R^{4e} , C_{3-8} alkenyl substituted with 0-3 R^{4e} , C_{3-8} alkynyl substituted with 0-3 R^{4e} ,
 25 a $(CH_2)_r-C_{3-6}$ carbocyclic residue substituted with 0-2 R^{4e} , and a $(CHR)_r-4-10$ membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-2 R^{4e} ;

30 R^{4c} is independently selected from $-C(O)R^{4b}$, $-C(O)OR^{4d}$, $-C(O)NR^{4f}R^{4f}$, and $(CH_2)_rphenyl$;

R^{4d} , at each occurrence, is selected from methyl, CF_3 ,
 C_{2-6} alkyl substituted with 0-3 R^{4e} , C_{3-8} alkenyl
substituted with 0-3 R^{4e} , C_{3-8} alkynyl substituted
with 0-3 R^{4e} , and a C_{3-10} carbocyclic residue
5 substituted with 0-3 R^{4e} ;

R^{4e} , at each occurrence, is selected from C_{1-6} alkyl, C_{2-8}
alkenyl, C_{2-8} alkynyl, $(CH_2)_r C_{3-6}$ cycloalkyl, Cl, F,
Br, I, CN, NO_2 , $(CF_2)_r CF_3$, $(CH_2)_r OC_{1-5}$ alkyl, OH, SH,
10 $(CH_2)_r SC_{1-5}$ alkyl, $(CH_2)_r NR^{4f} R^{4f}$, $-C(O)R^{4i}$, $-C(O)OR^{4j}$,
 $-C(O)NR^{4h} R^{4h}$, $-OC(O)NR^{4h} R^{4h}$, $-NR^{4h} C(O)NR^{4h} R^{4h}$,
 $-NR^{4h} C(O)OR^{4j}$, and $(CH_2)_r$ phenyl;

R^{4f} , at each occurrence, is selected from H, C_{1-6} alkyl,
15 C_{3-6} cycloalkyl, and phenyl;

R^{4h} , at each occurrence, is independently selected from H,
 C_{1-6} alkyl, C_{3-8} alkenyl, C_{3-8} alkynyl, and a $(CH_2)_r$ -
 C_{3-10} carbocyclic;

20 R^{4i} , at each occurrence, is selected from H, C_{1-6} alkyl,
 C_{3-8} alkenyl, C_{3-8} alkynyl, and a $(CH_2)_r$ - C_{3-6}
carbocyclic residue;

25 R^{4j} , at each occurrence, is selected from CF_3 , C_{1-6} alkyl,
 C_{3-8} alkenyl, C_{3-8} alkynyl, and a C_{3-10} carbocyclic
residue;

30 R^5 , at each occurrence, is independently selected from H,
 $=O$, C_{1-6} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, $(CRR)_r OH$,
 $(CRR)_r SH$, $(CRR)_r OR^{5d}$, $(CRR)_r SR^{5d}$, $(CRR)_r NR^{5a} R^{5a}$,
 $(CRR)_r C(O)OH$, $(CRR)_r C(O)R^{5b}$, $(CRR)_r C(O)NR^{5a} R^{5a}$,
 $(CRR)_r NR^{5a} C(O)R^{5b}$, $(CRR)_r OC(O)NR^{5a} R^{5a}$,
 $(CRR)_r NR^{5a} C(O)OR^{5d}$, $(CRR)_r NR^{5a} C(O)NR^{5a} R^{5a}$,

(CRR)_rNR^{5a}C(O)H, (CRR)_rC(O)OR^{5d}, (CRR)_rOC(O)R^{5b},
 (CRR)_rS(O)_pR^{5b}, (CRR)_rS(O)₂NR^{5a}R^{5a}, (CRR)_rNR^{5a}S(O)₂R^{5b},
 (CRR)_rNR^{5a}S(O)₂NR^{5a}R^{5a}, C₁₋₆ haloalkyl, a (CRR)_r-C₃₋₁₀
 carbocyclic residue substituted with 0-3 R^{5c}, and a
 5 (CRR)_r-5-10 membered heterocyclic system containing
 1-4 heteroatoms selected from N, O, and S,
 substituted with 0-2 R^{5c};

R^{5a}, at each occurrence, is independently selected from H,
 10 methyl substituted with 0-1 R^{5g}, C₂₋₆ alkyl
 substituted with 0-2 R^{5e}, C₃₋₈ alkenyl substituted
 with 0-2 R^{5e}, C₃₋₈ alkynyl substituted with 0-2 R^{5e},
 a (CH₂)_r-C₃₋₁₀ carbocyclic residue substituted with
 0-5 R^{5e}, and a (CH₂)_r-5-10 membered heterocyclic
 15 system containing 1-4 heteroatoms selected from N,
 O, and S, substituted with 0-3 R^{5e};

R^{5b}, at each occurrence, is selected from C₁₋₆ alkyl
 substituted with 0-3 R^{5e}, C₃₋₈ alkenyl substituted
 20 with 0-2 R^{5e}, C₃₋₈ alkynyl substituted with 0-2 R^{5e},
 a (CH₂)_r-C₃₋₆ carbocyclic residue substituted with
 0-2 R^{5e}, and a (CH₂)_r-5-6 membered heterocyclic
 system containing 1-4 heteroatoms selected from N,
 O, and S, substituted with 0-3 R^{5e};

25 R^{5c}, at each occurrence, is selected from C₁₋₆ alkyl, C₂₋₈
 alkenyl, C₂₋₈ alkynyl, (CH₂)_rC₃₋₆ cycloalkyl, Cl, Br,
 I, F, (CF₂)_rCF₃, NO₂, CN, (CH₂)_rNR^{5f}R^{5f}, (CH₂)_rOH,
 (CH₂)_rOC₁₋₄ alkyl, (CH₂)_rSC₁₋₄ alkyl, (CH₂)_rC(O)OH,
 30 (CH₂)_rC(O)R^{5b}, (CH₂)_rC(O)NR^{5f}R^{5f}, (CH₂)_rOC(O)NR^{5f}R^{5f},
 (CH₂)_rNR^{5f}C(O)R^{5b}, (CH₂)_rC(O)OC₁₋₄ alkyl,
 (CH₂)_rNR^{5f}C(O)OC₁₋₄ alkyl, (CH₂)_rOC(O)R^{5b},
 (CH₂)_rC(=NR^{5f})NR^{5f}R^{5f}, (CH₂)_rS(O)_pR^{5b},

$(\text{CH}_2)_r\text{NHC}(=\text{NR}^{5f})\text{NR}^{5f}\text{R}^{5f}$, $(\text{CH}_2)_r\text{S}(\text{O})_2\text{NR}^{5f}\text{R}^{5f}$,
 $(\text{CH}_2)_r\text{NR}^{5f}\text{S}(\text{O})_2\text{R}^{5b}$, and $(\text{CH}_2)_r\text{phenyl}$ substituted with
 0-3 R^{5e} ;

5 R^{5d} , at each occurrence, is selected from methyl, CF_3 ,
 C_{2-6} alkyl substituted with 0-2 R^{5e} , C_{3-8} alkenyl
 substituted with 0-2 R^{5e} , C_{3-8} alkynyl substituted
 with 0-2 R^{5e} , and a C_{3-10} carbocyclic residue
 substituted with 0-3 R^{5e} ;

10

R^{5e} , at each occurrence, is selected from C_{1-6} alkyl, C_{2-8}
 alkenyl, C_{2-8} alkynyl, C_{3-6} cycloalkyl, Cl, F, Br, I,
 CN, NO_2 , $(\text{CF}_2)_r\text{CF}_3$, $(\text{CH}_2)_r\text{OC}_{1-5}$ alkyl, OH, SH,
 $(\text{CH}_2)_r\text{SC}_{1-5}$ alkyl, $(\text{CH}_2)_r\text{NR}^{5f}\text{R}^{5f}$, and $(\text{CH}_2)_r\text{phenyl}$;

15

R^{5f} , at each occurrence, is selected from H, C_{1-6} alkyl,
 and C_{3-6} cycloalkyl;

20

R^{5g} is independently selected from $-\text{C}(\text{O})\text{R}^{5b}$, $-\text{C}(\text{O})\text{OR}^{5d}$,
 $-\text{C}(\text{O})\text{NR}^{5f}\text{R}^{5f}$, and $(\text{CH}_2)_r\text{phenyl}$;

25

R, at each occurrence, is selected from H, C_{1-6} alkyl
 substituted with R^{5e} , C_{2-8} alkenyl, C_{2-8} alkynyl,
 $(\text{CH}_2)_r\text{C}_{3-6}$ cycloalkyl, and $(\text{CH}_2)_r\text{phenyl}$ substituted
 with R^{5e} ;

30

R^6 , at each occurrence, is selected from C_{1-8} alkyl, C_{2-8}
 alkenyl, C_{2-8} alkynyl, $(\text{CH}_2)_r\text{C}_{3-6}$ cycloalkyl, Cl, Br,
 I, F, NO_2 , CN, $(\text{CR}'\text{R}')_r\text{NR}^{6a}\text{R}^{6a}$, $(\text{CR}'\text{R}')_r\text{OH}$,
 $(\text{CR}'\text{R}')_r\text{O}(\text{CR}'\text{R}')_r\text{R}^{6d}$, $(\text{CR}'\text{R}')_r\text{SH}$, $(\text{CR}'\text{R}')_r\text{C}(\text{O})\text{H}$,
 $(\text{CR}'\text{R}')_r\text{S}(\text{CR}'\text{R}')_r\text{R}^{6d}$, $(\text{CR}'\text{R}')_r\text{SC}(\text{O})(\text{CR}'\text{R}')_r\text{R}^{6b}$,
 $(\text{CR}'\text{R}')_r\text{C}(\text{O})\text{OH}$, $(\text{CR}'\text{R}')_r\text{C}(\text{O})(\text{CR}'\text{R}')_r\text{R}^{6b}$,
 $(\text{CR}'\text{R}')_r\text{NR}^{6a}\text{R}^{6a}$, $(\text{CR}'\text{R}')_r\text{C}(\text{O})\text{NR}^{6a}\text{R}^{6a}$,

$(\text{CR}'\text{R}')_r\text{NR}^{6f}\text{C}(\text{O})(\text{CR}'\text{R}')_r\text{R}^{6b}$, $(\text{CR}'\text{R}')_r\text{C}(\text{O})\text{O}(\text{CR}'\text{R}')_r\text{R}^{6d}$,
 $(\text{CR}'\text{R}')_r\text{OC}(\text{O})(\text{CR}'\text{R}')_r\text{R}^{6b}$,
 $(\text{CR}'\text{R}')_r\text{OC}(\text{O})\text{NR}^{6a}(\text{CR}'\text{R}')_r\text{R}^{6d}$,
 $(\text{CR}'\text{R}')_r\text{NR}^{6a}\text{C}(\text{O})\text{NR}^{6a}(\text{CR}'\text{R}')_r\text{R}^{6d}$,
5 $(\text{CR}'\text{R}')_r\text{NR}^{6a}\text{C}(\text{S})\text{NR}^{6a}(\text{CR}'\text{R}')_r\text{R}^{6d}$,
 $(\text{CR}'\text{R}')_r\text{NR}^{6f}\text{C}(\text{O})\text{O}(\text{CR}'\text{R}')_r\text{R}^{6b}$, $(\text{CR}'\text{R}')_r\text{C}(=\text{NR}^{6f})\text{NR}^{6a}\text{R}^{6a}$,
 $(\text{CR}'\text{R}')_r\text{NHC}(=\text{NR}^{6f})\text{NR}^{6f}\text{R}^{6f}$, $(\text{CR}'\text{R}')_r\text{S}(\text{O})_p(\text{CR}'\text{R}')_r\text{R}^{6b}$,
 $(\text{CR}'\text{R}')_r\text{S}(\text{O})_2\text{NR}^{6a}\text{R}^{6a}$, $(\text{CR}'\text{R}')_r\text{NR}^{6f}\text{S}(\text{O})_2\text{NR}^{6a}\text{R}^{6a}$,
 $(\text{CR}'\text{R}')_r\text{NR}^{6f}\text{S}(\text{O})_2(\text{CR}'\text{R}')_r\text{R}^{6b}$, C_{1-6} haloalkyl, C_{2-8}
10 alkenyl substituted with 0-3 R' , C_{2-8} alkynyl
substituted with 0-3 R' , $(\text{CR}'\text{R}')_r$ phenyl substituted
with 0-3 R^{6e} , and a $(\text{CH}_2)_r$ -5-6 membered heterocyclic
system containing 1-2 heteroatoms selected from N,
O, and S, substituted with 0-2 R^{6e} ;

15

alternatively, two R^6 on adjacent atoms on R^1 may join to
form a cyclic acetal;

R^{6a} , at each occurrence, is selected from H, methyl
20 substituted with 0-1 R^{6g} , C_{2-6} alkyl substituted with
0-2 R^{6e} , C_{3-8} alkenyl substituted with 0-2 R^{6e} , C_{3-8}
alkynyl substituted with 0-2 R^{6e} , a $(\text{CH}_2)_r$ - C_{3-10}
carbocyclic residue substituted with 0-5 R^{6e} , and a
 $(\text{CH}_2)_r$ -5-10 membered heterocyclic system containing
25 1-4 heteroatoms selected from N, O, and S,
substituted with 0-2 R^{6e} ;

R^{6b} , at each occurrence, is selected from H, C_{1-6} alkyl
substituted with 0-2 R^{6e} , C_{3-8} alkenyl substituted
30 with 0-2 R^{6e} , C_{3-8} alkynyl substituted with 0-2 R^{6e} ,
a $(\text{CH}_2)_r$ - C_{3-6} carbocyclic residue substituted with 0-3
 R^{6e} , and a $(\text{CH}_2)_r$ -5-6 membered heterocyclic system

containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-2 R^{6e};

R^{6d}, at each occurrence, is selected from C₃₋₈ alkenyl
 5 substituted with 0-2 R^{6e}, C₃₋₈ alkynyl substituted
 with 0-2 R^{6e}, methyl, CF₃, C₂₋₆ alkyl substituted
 with 0-3 R^{6e}, C₂₋₄ haloalkyl, a (CH₂)_r-C₃₋₁₀
 carbocyclic residue substituted with 0-3 R^{6e}, and a
 (CH₂)_r-5-6 membered heterocyclic system containing
 10 1-4 heteroatoms selected from N, O, and S,
 substituted with 0-3 R^{6e};

R^{6e}, at each occurrence, is selected from C₁₋₆ alkyl, C₂₋₈
 alkenyl, C₂₋₈ alkynyl, (CH₂)_r-C₃₋₆ cycloalkyl, Cl, F,
 15 Br, I, CN, NO₂, (CF₂)_rCF₃, (CH₂)_rOC₁₋₅ alkyl, OH, SH,
 (CH₂)_rSC₁₋₅ alkyl, (CH₂)_rNR^{6f}R^{6f}, and (CH₂)_rphenyl;

R^{6f}, at each occurrence, is selected from H, C₁₋₅ alkyl,
 and C₃₋₆ cycloalkyl, and phenyl;

20

R^{6g} is independently selected from -C(O)R^{6b}, -C(O)OR^{6d},
 -C(O)NR^{6f}R^{6f}, and (CH₂)_rphenyl;

R⁷, at each occurrence, is selected from C₁₋₈ alkyl, C₂₋₈
 25 alkenyl, C₂₋₈ alkynyl, (CH₂)_r-C₃₋₆ cycloalkyl, Cl, Br,
 I, F, NO₂, CN, (CR'R')_rNR^{7a}R^{7a}, (CR'R')_rOH,
 (CR'R')_rO(CR'R')_rR^{7d}, (CR'R')_rSH, (CR'R')_rC(O)H,
 (CR'R')_rS(CR'R')_rR^{7d}, (CR'R')_rC(O)OH,
 (CR'R')_rC(O)(CR'R')_rR^{7b}, (CR'R')_rC(O)NR^{7a}R^{7a},
 30 (CR'R')_rNR^{7f}C(O)(CR'R')_rR^{7b}, (CR'R')_rC(O)O(CR'R')_rR^{7d},
 (CR'R')_rOC(O)(CR'R')_rR^{7b},
 (CR'R')_rOC(O)NR^{7a}(CR'R')_rR^{7a},
 (CR'R')_rNR^{7a}C(O)NR^{7a}(CR'R')_rR^{7a},

$(CR'R')_rNR^{7f}C(O)O(CR'R')_rR^{7d}$, $(CR'R')_rC(=NR^{7f})NR^{7a}R^{7a}$,
 $(CR'R')_rNHC(=NR^{7f})NR^{7f}R^{7f}$, $(CR'R')_rS(O)_p(CR'R')_rR^{7b}$,
 $(CR'R')_rS(O)_2NR^{7a}R^{7a}$, $(CR'R')_rNR^{7a}S(O)_2NR^{7a}R^{7a}$,
 $(CR'R')_rNR^{7f}S(O)_2(CR'R')_rR^{7b}$, C₁₋₆ haloalkyl, C₂₋₈
5 alkenyl substituted with 0-3 R', C₂₋₈ alkynyl
substituted with 0-3 R', and (CR'R')_rphenyl
substituted with 0-3 R^{7e};

10 alternatively, two R⁷ on adjacent atoms on R² may join to
form a cyclic acetal;

R^{7a}, at each occurrence, is independently selected from H,
methyl substituted with 0-1 R^{7g}, C₂₋₆ alkyl
substituted with 0-2 R^{7e}, C₃₋₈ alkenyl substituted
15 with 0-2 R^{7e}, C₃₋₈ alkynyl substituted with 0-2 R^{7e},
a (CH₂)_r-C₃₋₁₀ carbocyclic residue substituted with
0-5 R^{7e}, and a (CH₂)_r-5-10 membered heterocyclic
system containing 1-4 heteroatoms selected from N,
O, and S, substituted with 0-2 R^{7e};

20 R^{7b}, at each occurrence, is selected from C₁₋₆ alkyl
substituted with 0-2 R^{7e}, C₃₋₈ alkenyl substituted
with 0-2 R^{7e}, C₃₋₈ alkynyl substituted with 0-2 R^{7e},
a (CH₂)_rC₃₋₆ carbocyclic residue substituted with 0-3
25 R^{7e}, and a (CH₂)_r-5-6 membered heterocyclic system
containing 1-4 heteroatoms selected from N, O, and
S, substituted with 0-2 R^{7e};

30 R^{7d}, at each occurrence, is selected from C₃₋₈ alkenyl
substituted with 0-2 R^{7e}, C₃₋₈ alkynyl substituted
with 0-2 R^{7e}, methyl, CF₃, C₂₋₄ haloalkyl, C₂₋₆ alkyl
substituted with 0-3 R^{7e}, a (CH₂)_r-C₃₋₁₀ carbocyclic
residue substituted with 0-3 R^{7e}, and a (CH₂)_r-5-6
membered heterocyclic system containing 1-4

heteroatoms selected from N, O, and S, substituted with 0-3 R^{7e};

5 R^{7e}, at each occurrence, is selected from C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, (CH₂)_rC₃₋₆ cycloalkyl, Cl, F, Br, I, CN, NO₂, (CF₂)_rCF₃, (CH₂)_rOC₁₋₅ alkyl, OH, SH, C(O)OC₁₋₅ alkyl, (CH₂)_rSC₁₋₅ alkyl, (CH₂)_rNR^{7f}R^{7f}, and (CH₂)_rphenyl;

10 R^{7f}, at each occurrence, is selected from H, C₁₋₅ alkyl, and C₃₋₆ cycloalkyl, and phenyl;

R^{7g} is independently selected from -C(O)R^{7b}, -C(O)OR^{7d}, -C(O)NR^{7f}R^{7f}, and (CH₂)_rphenyl;

15

R', at each occurrence, is selected from H, C₁₋₆ alkyl substituted with R^{6e}, C₂₋₈ alkenyl, C₂₋₈ alkynyl, (CH₂)_rC₃₋₆ cycloalkyl, and (CH₂)_rphenyl substituted with R^{6e};

20

R⁸ is selected from H, C₁₋₄ alkyl, and C₃₋₄ cycloalkyl;

R⁹ is selected from H, C₁₋₄ alkyl, C₃₋₄ cycloalkyl, -C(O)H, and -C(O)-C₁₋₄alkyl;

25

R¹⁰ is independently selected from H, and C₁₋₄alkyl substituted with 0-1 R^{10b};

30 R^{10b}, at each occurrence, is independently selected from -OH, -SH, -NR^{10c}R^{10c}, -C(O)NR^{10c}R^{10c}, and -NHC(O)R^{10c};

R^{10c} is selected from H, C₁₋₄ alkyl and C₃₋₆ cycloalkyl;

R^{11} is selected from H, C_{1-4} alkyl, $(CHR)_qOH$, $(CHR)_qSH$,
 $(CHR)_qOR^{11d}$, $(CHR)_qS(O)_pR^{11d}$, $(CHR)_rC(O)R^{11b}$,
 $(CHR)_rNR^{11a}R^{11a}$, $(CHR)_rC(O)NR^{11a}R^{11a}$,
 $(CHR)_rC(O)NR^{11a}OR^{11d}$, $(CHR)_qNR^{11a}C(O)R^{11b}$,
5 $(CHR)_qNR^{11a}C(O)OR^{11d}$, $(CHR)_qOC(O)NR^{11a}R^{11a}$,
 $(CHR)_rC(O)OR^{11d}$, a $(CHR)_r-C_{3-6}$ carbocyclic residue
substituted with 0-5 R^{11e} , and a $(CHR)_r-5-10$ membered
heterocyclic system containing 1-4 heteroatoms
selected from N, O, and S, substituted with 0-3 R^{11e} ;
10
 R^{11a} , at each occurrence, is independently selected from
H, C_{1-4} alkyl, C_{3-4} alkenyl, C_{3-4} alkynyl, $(CH_2)_rC_{3-6}$
cycloalkyl, a $(CH_2)_r-C_{3-6}$ carbocyclic residue
substituted with 0-5 R^{11e} , and a $(CH_2)_r-5-6$ membered
15 heterocyclic system containing 1-4 heteroatoms
selected from N, O, and S, substituted with 0-3 R^{11e} ;

 R^{11b} , at each occurrence, is independently selected from
 C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, a $(CH_2)_r-C_{3-6}$
20 carbocyclic residue substituted with 0-2 R^{11e} , and a
 $(CH_2)_r-5-6$ membered heterocyclic system containing
1-4 heteroatoms selected from N, O, and S,
substituted with 0-3 R^{11e} ;

25 R^{11d} , at each occurrence, is independently selected from
H, methyl, $-CF_3$, C_{2-4} alkyl, C_{3-6} alkenyl, C_{3-6}
alkynyl, a C_{3-6} carbocyclic residue substituted with
0-3 R^{11e} , and a $(CH_2)_r-5-6$ membered heterocyclic
system containing 1-4 heteroatoms selected from N,
30 O, and S, substituted with 0-3 R^{11e} ;

R^{11e}, at each occurrence, is selected from C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₆ cycloalkyl, Cl, F, Br, I, CN, NO₂, (CF₂)_rCF₃, (CH₂)_rOC₁₋₅ alkyl, OH, -O-C₁₋₆ alkyl, SH, (CH₂)_rSC₁₋₅ alkyl, (CH₂)_rNR^{11f}R^{11f}, and
 5 (CH₂)_rphenyl;

R^{11f}, at each occurrence, is selected from H, C₁₋₆ alkyl, and C₃₋₆ cycloalkyl;

10 R¹² is selected from H, C₁₋₄ alkyl, (CHR)_qOH, (CHR)_qSH, (CHR)_qOR^{12d}, (CHR)_qS(O)_pR^{12d}, (CHR)_rC(O)R^{12b}, (CHR)_rNR^{12a}R^{12a}, (CHR)_rC(O)NR^{12a}R^{12a}, (CHR)_rC(O)NR^{12a}OR^{12d}, (CHR)_qNR^{12a}C(O)R^{12b}, (CHR)_qNR^{12a}C(O)OR^{12d}, (CHR)_qOC(O)NR^{12a}R^{12a},
 15 (CHR)_rC(O)OR^{12d}, a (CHR)_r-C₃₋₆ carbocyclic residue substituted with 0-5 R^{12e}, and a (CHR)_r-5-10 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{12e};

20 R^{12a}, at each occurrence, is independently selected from H, C₁₋₄ alkyl, C₃₋₄ alkenyl, C₃₋₄ alkynyl, (CH₂)_rC₃₋₆ cycloalkyl, a (CH₂)_r-C₃₋₆ carbocyclic residue substituted with 0-5 R^{12e}, and a (CH₂)_r-5-6 membered heterocyclic system containing 1-4 heteroatoms
 25 selected from N, O, and S, substituted with 0-3 R^{12e};

R^{12b}, at each occurrence, is independently selected from C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, a (CH₂)_r-C₃₋₆ carbocyclic residue substituted with 0-2 R^{12e}, and a
 30 (CH₂)_r-5-6 membered heterocyclic system containing

1-4 heteroatoms selected from N, O, and S,
substituted with 0-3 R^{12e};

R^{12d}, at each occurrence, is independently selected from
5 H, methyl, -CF₃, C₂₋₄ alkyl, C₃₋₆ alkenyl, C₃₋₆
alkynyl, a C₃₋₆ carbocyclic residue substituted with
0-3 R^{12e}, and a (CH₂)_{r-5-6} membered heterocyclic
system containing 1-4 heteroatoms selected from N,
O, and S, substituted with 0-3 R^{12e};

10

R^{12e}, at each occurrence, is selected from C₁₋₆ alkyl, C₂₋₈
alkenyl, C₂₋₈ alkynyl, C₃₋₆ cycloalkyl, Cl, F, Br, I,
CN, NO₂, (CF₂)_rCF₃, (CH₂)_rOC₁₋₅ alkyl, OH, -O-C₁₋₆
alkyl, SH, (CH₂)_rSC₁₋₅ alkyl, (CH₂)_rNR^{12f}R^{12f}, and
15 (CH₂)_rphenyl;

R^{12f}, at each occurrence, is selected from H, C₁₋₆ alkyl,
and C₃₋₆ cycloalkyl;

20 R¹³, at each occurrence, is independently selected from H,
and C₁₋₄alkyl substituted with 0-1 R^{13b}, -OH, -NH₂,
F, Cl, Br, I, -OR^{13a}, -N(R^{13a})₂, and C₁₋₄ alkyl
substituted with 0-3 R^{13b};

25 R^{13a} is selected from H, C₁₋₄ alkyl and C₃₋₆ cycloalkyl;

R^{13b}, at each occurrence, is independently selected from
-OH, -SH, -NR^{13c}R^{13c}, -C(O)NR^{13c}R^{13c}, and -NHC(O)R^{13c};

30 R^{13c} is selected from H, C₁₋₄ alkyl and C₃₋₆ cycloalkyl;

R¹⁴, at each occurrence, is independently selected from H
and C₁₋₄alkyl;

alternatively, two R¹⁴s, along with the carbon atom to
5 which they are attached, join to form a C₃₋₆
carbocyclic ring;

R¹⁵, at each occurrence, is independently selected from H,
C₁₋₄alkyl, OH, NH₂, -O-C₁₋₄ alkyl, NR^{15a}R^{15a},
10 C(O)NR^{15a}R^{15a}, NR^{15a}C(O)R^{15b}, NR^{15a}C(O)OR^{15d},
OC(O)NR^{15a}R^{15a}, and (CHR)_rC(O)OR^{15d};

alternatively, two R¹⁵s, along with the carbon atom or
atoms to which they are attached, join to form a C₃₋₆
15 carbocyclic ring;

R^{15a}, at each occurrence, is independently selected from
H, and C₁₋₄ alkyl;

20 R^{15b}, at each occurrence, is independently selected from
C₁₋₄ alkyl, C₃₋₆ alkenyl, and C₃₋₆ alkynyl;

R^{15d}, at each occurrence, is independently selected from
C₁₋₄ alkyl, C₃₋₆ alkenyl, and C₃₋₆ alkynyl;

25 R¹⁶ is selected from C₁₋₄ alkyl;

l is selected from 1, 2 and 3;

30 n is selected from 0, 1, 2, and 3;

m is selected from 0 and 1;

p, at each occurrence, is independently selected from 0,
1, and 2;

5 q, at each occurrence, is independently selected from 1,
2, 3, and 4;

r, at each occurrence, is independently selected from 0,
1, 2, 3, and 4;

10

t, at each occurrence, is independently selected from 2,
3, and 4;

s is selected from 0 and 1.

15

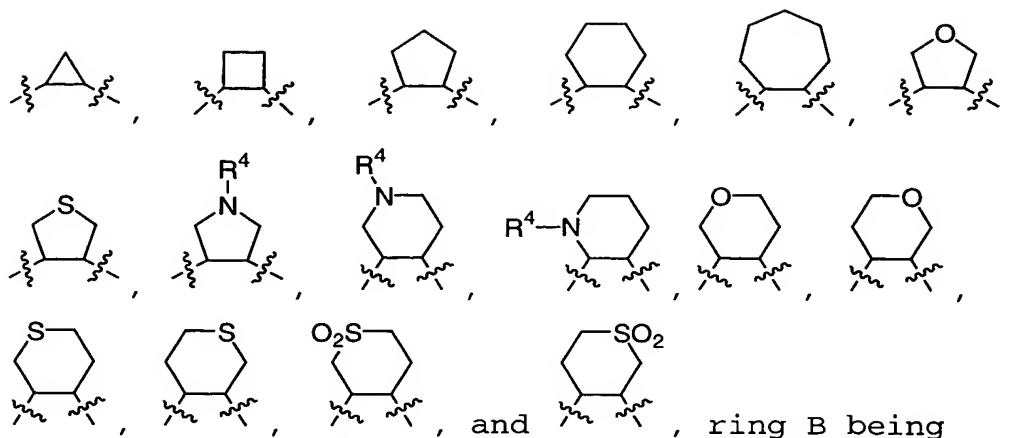
[3] Thus, in a another embodiment, the present
invention provides novel compounds of formula (I):

m is 0.

20

In another embodiment, the present invention
provides novel compounds of formula (I), wherein:

ring B is selected from



5 optionally substituted with 0-1 R^5 ; and

R^{11} and R^{12} are H.

10 In another embodiment, the present invention provides novel compounds of formula (I), wherein:

R^5 , at each occurrence, is independently selected from H, C_{1-6} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, $(CRR)_rOH$, $(CRR)_rSH$, $(CRR)_rOR^{5d}$, $(CRR)_rSR^{5d}$, $(CRR)_rNR^{5a}R^{5a}$,
 15 $(CRR)_rC(O)OH$, $(CRR)_rC(O)R^{5b}$, $(CRR)_rC(O)NR^{5a}R^{5a}$, $(CRR)_rNR^{5a}C(O)R^{5b}$, $(CRR)_rNR^{5a}C(O)OR^{5d}$, $(CRR)_rOC(O)NR^{5a}R^{5a}$, $(CHR)_rNR^{5a}C(O)NR^{5a}R^{5a}$, $CRR(CRR)_rNR^{5a}C(O)H$, $(CRR)_rC(O)OR^{5b}$, $(CRR)_rOC(O)R^{5b}$, $(CRR)_rS(O)_pR^{5b}$, $(CRR)_rS(O)_2NR^{5a}R^{5a}$, $(CRR)_rNR^{5a}S(O)_2R^{5b}$,
 20 and C_{1-6} haloalkyl;

R^{5a} , at each occurrence, is independently selected from H, methyl, C_{1-6} alkyl substituted with 0-2 R^{5e} wherein the alkyl is selected from ethyl, propyl, i-propyl,
 25 butyl, i-butyl, pentyl, hexyl, C_3 alkenyl substituted with 0-1 R^{5e} , wherein the alkenyl is selected from allyl, C_3 alkynyl substituted with 0-1 R^{5e} wherein the alkynyl is selected from propynyl, and a

(CH₂)_r-C₃₋₄ carbocyclic residue substituted with 0-5 R^{5e}, wherein the carbocyclic residue is selected from cyclopropyl, and cyclobutyl;

5 R^{5b}, at each occurrence, is selected from C₁₋₆ alkyl substituted with 0-2 R^{5e}, wherein the alkyl is selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, pentyl, and hexyl, a (CH₂)_r-C₃₋₄ carbocyclic residue substituted with 0-2 R^{5e}, wherein
10 the carbocyclic residue is selected from cyclopropyl, and cyclobutyl; and

R^{5d}, at each occurrence, is selected from methyl, CF₃, C₂₋₆ alkyl substituted with 0-2 R^{5e}, wherein the
15 alkyl is selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, pentyl, and hexyl, C₃₋₈ alkenyl, C₃₋₈ alkynyl, and a C₃₋₁₀ carbocyclic residue substituted with 0-3 R^{5e}.

20 In another embodiment, the present invention provides novel compounds of formula (I), wherein:

R⁵, at each occurrence, is independently selected from H, C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, (CRR)_rOH,
25 (CRR)_rSH, (CRR)_rOR^{5d}, (CRR)_rSR^{5d}, (CRR)_rNR^{5a}R^{5a}, (CRR)_rN(O)R^{5a}R^{5a}, N₃, (CRR)_rC(O)OH, (CRR)_rC(O)R^{5b}, (CRR)_rC(O)NR^{5a}R^{5a}, (CRR)_rNR^{5a}C(O)R^{5b}, (CRR)_rNR^{5a}C(O)OR^{5d}, (CRR)_rOC(O)NR^{5a}R^{5a}, (CHR)_rNR^{5a}C(O)NR^{5a}R^{5a}, CRR(CRR)_rNR^{5a}C(O)H,
30 (CRR)_rC(O)OR^{5b}, (CRR)_rOC(O)R^{5b}, (CRR)_rS(O)_pR^{5b}, (CRR)_rS(O)₂NR^{5a}R^{5a}, (CRR)_rNR^{5a}S(O)₂R^{5b}, and C₁₋₆ haloalkyl;

R^{5a}, at each occurrence, is independently selected from H, methyl, C₁₋₆ alkyl substituted with 0-2 R^{5e} wherein the alkyl is selected from ethyl, propyl, i-propyl, butyl, i-butyl, pentyl, hexyl, C₃ alkenyl substituted with 0-1 R^{5e}, wherein the alkenyl is selected from allyl, C₃ alkynyl substituted with 0-1 R^{5e} wherein the alkynyl is selected from propynyl, and a (CH₂)_r-C₃₋₄ carbocyclic residue substituted with 0-5 R^{5e}, wherein the carbocyclic residue is selected from cyclopropyl, and cyclobutyl;

R^{5b}, at each occurrence, is selected from C₁₋₆ alkyl substituted with 0-2 R^{5e}, wherein the alkyl is selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, pentyl, and hexyl, a (CH₂)_r-C₃₋₄ carbocyclic residue substituted with 0-2 R^{5e}, wherein the carbocyclic residue is selected from cyclopropyl, and cyclobutyl; and

R^{5d}, at each occurrence, is selected from methyl, CF₃, C₂₋₆ alkyl substituted with 0-2 R^{5e}, wherein the alkyl is selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, pentyl, and hexyl, C₃₋₈ alkenyl, C₃₋₈ alkynyl, and a C₃₋₁₀ carbocyclic residue substituted with 0-3 R^{5e}.

In another embodiment, the present invention provides novel compounds of formula (I), wherein:

R⁴ is selected from H, C₁₋₆ alkyl, C₃₋₈ alkenyl, C₃₋₈ alkynyl, (CRR)_qOH, (CRR)_tSH, (CRR)_tOR^{4d}, (CRR)_tSR^{4d}, (CRR)_tNR^{4a}R^{4a}, (CRR)_qC(O)OH, (CRR)_rC(O)R^{4b}, (CRR)_rC(O)NR^{4a}R^{4a}, (CRR)_tNR^{4a}C(O)R^{4b}, (CRR)_tOC(O)NR^{4a}R^{4a}, (CRR)_tNR^{4a}C(O)OR^{4d},

$(\text{CRR})_t \text{NR}^{4a} \text{C}(\text{O}) \text{R}^{4b}$, $(\text{CRR})_r \text{C}(\text{O}) \text{OR}^{4b}$, $(\text{CRR})_t \text{OC}(\text{O}) \text{R}^{4b}$,
 $(\text{CRR})_r \text{S}(\text{O})_p \text{R}^{4b}$, $(\text{CRR})_r \text{S}(\text{O})_2 \text{NR}^{4a} \text{R}^{4a}$, $(\text{CRR})_r \text{NR}^{4a} \text{S}(\text{O})_2 \text{R}^{4b}$;

5 R, at each occurrence, is independently selected from H,
 methyl, ethyl, propyl, allyl, propynyl, $(\text{CH}_2)_r \text{C}_{3-6}$
 cycloalkyl, and $(\text{CH}_2)_r$ phenyl substituted with R^{6e} ;

10 R^5 , at each occurrence, is independently selected from H,
 methyl, ethyl, propyl, i-propyl, butyl, i-butyl,
 allyl, propynyl, $(\text{CH}_2)_r \text{OH}$, $(\text{CH}_2)_r \text{OR}^{5d}$, $(\text{CH}_2)_r \text{NR}^{5a} \text{R}^{5a}$,
 $(\text{CH}_2)_r \text{C}(\text{O}) \text{OH}$, $(\text{CH}_2)_r \text{C}(\text{O}) \text{R}^{5b}$, $(\text{CH}_2)_r \text{C}(\text{O}) \text{NR}^{5a} \text{R}^{5a}$,
 $(\text{CH}_2)_r \text{NR}^{5a} \text{C}(\text{O}) \text{R}^{5b}$, $(\text{CH}_2)_r \text{OC}(\text{O}) \text{NR}^{5a} \text{R}^{5a}$,
 $(\text{CH}_2)_r \text{NR}^{5a} \text{C}(\text{O}) \text{OR}^{5d}$, $(\text{CH}_2)_r \text{NR}^{5a} \text{C}(\text{O}) \text{R}^{5b}$, $(\text{CH}_2)_r \text{C}(\text{O}) \text{OR}^{5b}$,
 $(\text{CH}_2)_r \text{OC}(\text{O}) \text{R}^{5b}$, $(\text{CH}_2)_r \text{NR}^{5a} \text{S}(\text{O})_2 \text{R}^{5b}$, and C_{1-6}
 15 haloalkyl;

R^{5a} , at each occurrence, is independently selected from H,
 methyl, ethyl, propyl, i-propyl, butyl, i-butyl,
 pentyl, hexyl, cyclopropyl, and cyclobutyl; and

20 r, at each occurrence, is selected from 0, 1, and 2.

In another embodiment, the present invention
 provides novel compounds of formula (I), wherein:

25 R^1 is selected from phenyl substituted with 0-2 R^6 ,
 naphthyl substituted with 0-2 R^6 , and a 5-10 membered
 heteroaryl system containing 1-4 heteroatoms
 selected from N, O, and S, substituted with 0-3 R^6
 30 wherein the heteroaryl is selected from indolyl,
 benzimidazolyl, benzofuranyl, benzothiofuranyl,
 benzoxazolyl, benzthiazolyl, benztriazolyl,
 benztetrazolyl, benzisoxazolyl, benzisothiazolyl,
 benzimidazalonyl, cinnolinyl, furanyl, imidazolyl,
 35 indazolyl, indolyl, isoquinolinyl, isothiazolyl,

isoxazolyl, oxazolyl, pyrazinyl, pyrazolyl,
 pyridazinyl, pyridyl, pyridinyl, pyrimidinyl,
 pyrrolyl, quinazolinyl, quinolinyl, thiazolyl,
 thienyl, and tetrazolyl;

5

R^2 is selected from phenyl substituted with 0-2 R^7 , and a
 5-10 membered heteroaryl system containing 1-4
 heteroatoms selected from N, O, and S, substituted
 with 0-3 R^7 wherein the heteroaryl is selected from
 10 indolyl, benzimidazolyl, benzofuranyl,
 benzothiofuranyl, benzoxazolyl, benzthiazolyl,
 benztriazolyl, benztetrazolyl, benzisoxazolyl,
 benzisothiazolyl, benzimidazolonyl, cinnolinyl,
 furanyl, imidazolyl, indazolyl, indolyl,
 15 isoquinolinyl isothiazolyl, isoxazolyl, oxazolyl,
 phthalazinyl, pyrazinyl, pyrazolyl, pyridazinyl,
 pyridyl, pyridinyl, pyrimidinyl, pyrrolyl,
 quinazolinyl, quinolinyl, thiazolyl, thienyl, and
 tetrazolyl;

20

R^4 is selected from H, methyl, ethyl, propyl, i-propyl,
 butyl, i-butyl, allyl, propynyl, $(CRR)_qOH$, $(CRR)_tSH$,
 $(CRR)_tOR^{4d}$, $(CRR)_tSR^{4d}$, $(CRR)_tNR^{4a}R^{4a}$, $(CRR)_qC(O)OH$,
 $(CRR)_rC(O)R^{4b}$, $(CRR)_rC(O)NR^{4a}R^{4a}$, $(CRR)_tNR^{4a}C(O)R^{4b}$,
 25 $(CRR)_tOC(O)NR^{4a}R^{4a}$, $(CRR)_tNR^{4a}C(O)OR^{4d}$,
 $(CRR)_tNR^{4a}C(O)R^{4b}$, $(CRR)_rC(O)OR^{4b}$, $(CRR)_tOC(O)R^{4b}$,
 $(CRR)_rS(O)_pR^{4b}$, $(CRR)_rS(O)_2NR^{4a}R^{4a}$, $(CRR)_rNR^{4a}S(O)_2R^{4b}$;

R^{4a} , at each occurrence, is independently selected from H,
 30 methyl substituted with 0-1 R^{4c} , C_{2-6} alkyl
 substituted with 0-3 R^{4e} wherein C_{2-6} is selected
 from ethyl, propyl, i-propyl, butyl, i-butyl,
 t-butyl, pentyl and hexyl, and a $(CH_2)_r-C_{3-6}$
 carbocyclic residue substituted with 0-4 R^{4e} wherein

the carbocyclic residue is selected from
cyclopropyl, cyclohexyl, and phenyl;

5 R^{4b} is selected from H, methyl, ethyl, propyl, i-propyl,
butyl, i-butyl, t-butyl, pentyl, and cyclopropyl;

10 R^{4d} is selected from methyl, ethyl, propyl, i-propyl,
butyl, i-butyl, t-butyl, pentyl, and cyclopropyl;
and

10 R^8 is selected from H, methyl, ethyl, propyl, i-propyl,
and cyclopropyl.

15 In another embodiment, the present invention
provides novel compounds of formula (I), wherein:

20 R^1 is selected from phenyl substituted with 0-2 R^6 ,
naphthyl substituted with 0-2 R^6 , and a 5-10
membered heteroaryl system containing 1-4
heteroatoms selected from N, O, and S, substituted
with 0-3 R^6 wherein the heteroaryl is selected from
indolyl, benzimidazolyl, benzofuranyl,
benzothiofuranyl, benzoxazolyl, benzthiazolyl,
benzo[b]thiophene, benztriazolyl, benztetrazolyl,
25 benzisoxazolyl, benzisothiazolyl, benzimidazalonyl,
cinnolinyl, furanyl, imidazolyl, indazolyl, indolyl,
isoquinolinyl, isothiazolyl, isoxazolyl, oxazolyl,
pyrazinyl, pyrazolyl, pyridazinyl, pyridyl,
pyrido[2,3-d]pyrimidinyl, pyrimido[5,4-
30 d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, pyridinyl,
pyrimidinyl, pyrrolyl, pyrrolo[2,1-
f][1,2,4]triazine, quinazolinyl, quinolinyl,
thiazolyl, thienyl, and tetrazolyl;

R^2 is selected from phenyl substituted with 0-2 R^7 , and a
 5-10 membered heteroaryl system containing 1-4
 heteroatoms selected from N, O, and S, substituted
 with 0-3 R^7 wherein the heteroaryl is selected from
 5 indolyl, benzimidazolyl, benzofuranyl,
 benzothiofuranyl, benzoxazolyl, benzthiazolyl,
 benzo[b]thiophene, benztriazolyl, benztetrazolyl,
 benzisoxazolyl, benzisothiazolyl, benzimidazalonyl,
 cinnolinyl, furanyl, imidazolyl, indazolyl, indolyl,
 10 isoquinolinyl isothiazolyl, isoxazolyl, oxazolyl,
 phthalazinyl, pyrazinyl, pyrazolyl, pyridazinyl,
 pyridyl, pyrido[2,3-d]pyrimidinyl, thieno[3,2-
 d]pyrimidinyl, pyridinyl, pyrimidinyl, pyrrolyl,
 pyrrolo[2,1-f][1,2,4]triazine, quinazolinyl,
 15 quinolinyl, thiazolyl, thienyl, and tetrazolyl;

R^4 is selected from H, methyl, ethyl, propyl, i-propyl,
 butyl, i-butyl, allyl, propynyl, $(CRR)_qOH$, $(CRR)_tSH$,
 $(CRR)_tOR^{4d}$, $(CRR)_tSR^{4d}$, $(CRR)_tNR^{4a}R^{4a}$, $(CRR)_qC(O)OH$,
 20 $(CRR)_rC(O)R^{4b}$, $(CRR)_rC(O)NR^{4a}R^{4a}$, $(CRR)_tNR^{4a}C(O)R^{4b}$,
 $(CRR)_tOC(O)NR^{4a}R^{4a}$, $(CRR)_tNR^{4a}C(O)OR^{4d}$,
 $(CRR)_tNR^{4a}C(O)R^{4b}$, $(CRR)_rC(O)OR^{4b}$, $(CRR)_tOC(O)R^{4b}$,
 $(CRR)_rS(O)_pR^{4b}$, $(CRR)_rS(O)_2NR^{4a}R^{4a}$, $(CRR)_rNR^{4a}S(O)_2R^{4b}$;

25 R^{4a} , at each occurrence, is independently selected from H,
 methyl substituted with 0-1 R^{4c} , C_{2-6} alkyl
 substituted with 0-3 R^{4e} wherein C_{2-6} is selected
 from ethyl, propyl, i-propyl, butyl, i-butyl,
 t-butyl, pentyl and hexyl, and a $(CH_2)_r-C_{3-6}$
 30 carbocyclic residue substituted with 0-4 R^{4e} wherein
 the carbocyclic residue is selected from
 cyclopropyl, cyclohexyl, and phenyl;

R^{4b} is selected from H, methyl, ethyl, propyl, i-propyl,
butyl, i-butyl, t-butyl, pentyl, and cyclopropyl;

5 R^{4d} is selected from methyl, ethyl, propyl, i-propyl,
butyl, i-butyl, t-butyl, pentyl, and cyclopropyl;
and

R⁸ is selected from H, methyl, ethyl, propyl, i-propyl,
and cyclopropyl.
10

In another embodiment, the present invention
provides novel compounds of formula (I), wherein:

15 R⁶, at each occurrence, is selected from C₁₋₈ alkyl, C₂₋₈
alkenyl, C₂₋₈ alkynyl, (CRR)_rC₃₋₆ cycloalkyl, Cl, Br,
I, F, NO₂, CN, (CRR)_rNR^{6a}R^{6a}, (CRR)_rOH,
(CRR)_rO(CRR)_rR^{6d}, (CRR)_rSH, (CRR)_rC(O)H,
(CRR)_rS(CRR)_rR^{6d}, (CRR)_rC(O)OH, (CRR)_rC(O)(CRR)_rR^{6b},
(CRR)_rC(O)NR^{6a}R^{6a}, (CRR)_rNR^{6f}C(O)(CRR)_rR^{6b},
20 (CRR)_rC(O)O(CRR)_rR^{6d}, (CRR)_rNR^{6a}C(O)NR^{6a}R^{6a},
(CRR)_rNR^{6a}C(S)NR^{6a}R^{6a}, (CRR)_rOC(O)(CRR)_rR^{6b},
(CRR)_rS(O)_p(CRR)_rR^{6b}, (CRR)_rS(O)₂NR^{6a}R^{6a},
(CRR)_rNR^{6f}S(O)₂(CRR)_rR^{6b}, (CRR)_rNR^{6f}S(O)₂NR^{6a}R^{6a}, C₁₋₆
haloalkyl, and (CRR)_rphenyl substituted with 0-3 R^{6e},
25 and a (CH₂)_{r-5-6} membered heterocyclic system
containing 1-2 heteroatoms selected from N, O, and
S, substituted with 0-2 R^{6e};

30 R^{6a}, at each occurrence, is independently selected from H,
methyl, ethyl, propyl, i-propyl, butyl, i-butyl,
t-butyl, pentyl, hexyl, cyclopropyl and phenyl;

35 R^{6b}, at each occurrence, is selected from methyl, ethyl,
propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl,
hexyl, cyclopropyl, and phenyl;

R^{6d}, at each occurrence, is selected from methyl, CF₃, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, hexyl, cyclopropyl, and phenyl;

5

R^{6e}, at each occurrence, is selected from C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, (CH₂)_rC₃₋₆ cycloalkyl, Cl, F, Br, I, CN, NO₂, (CF₂)_rCF₃, (CH₂)_rOC₁₋₅ alkyl, OH, SH, (CH₂)_rSC₁₋₅ alkyl, (CH₂)_rNR^{6f}R^{6f}, and (CH₂)_rphenyl;

10

R^{6f}, at each occurrence, is selected from H, methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, hexyl, cyclopropyl, and phenyl;

15 R⁷ is selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, s-butyl, t-butyl, pentyl, hexyl, (CRR)_rC₃₋₆ cycloalkyl, Cl, Br, I, F, NO₂, CN, (CRR)_rNR^{7a}R^{7a}, (CRR)_rOH, (CRR)_rO(CH)_rR^{7d}, (CRR)_rSH, (CRR)_rC(O)H, (CRR)_rS(CRR)_rR^{7d}, (CRR)_rC(O)OH, (CRR)_rC(O)(CRR)_rR^{7b}, (CRR)_rC(O)NR^{7a}R^{7a}, (CRR)_rNR^{7f}C(O)(CRR)_rR^{7b}, (CRR)_rC(O)O(CRR)_rR^{7d}, (CRR)_rOC(O)(CRR)_rR^{7b}, (CRR)_rNR^{7a}C(O)NR^{7a}R^{7a}, (CRR)_rNR^{7a}C(O)O(CRR)_rR^{7d}, (CRR)_rS(O)_p(CRR)_rR^{7b}, (CRR)_rS(O)₂NR^{7a}R^{7a}, (CRR)_rNR^{7f}S(O)₂(CRR)_rR^{7b}, C₁₋₆ haloalkyl, and (CRR)_rphenyl substituted with 0-3 R^{7e};

25

R^{7a}, at each occurrence, is selected from H, methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, hexyl, prop-2-enyl, 2-methyl-2-propenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, CH₂cyclopropyl, and benzyl;

30

R^{7b}, at each occurrence, is selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, hexyl, cyclopropyl, cyclopentyl, CH₂-cyclopentyl,

35

cyclohexyl, CH₂-cyclohexyl, CF₃, pyrrolidinyl, morpholinyl, piperizenyl substituted with 0-1 R^{7e}, and azetidiny;

5 R^{7d}, at each occurrence, is selected from methyl, CF₃, CF₂CF₃, CHF₂, CH₂F, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, hexyl, and cyclopropyl;

10 R^{7e}, at each occurrence, is selected from C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, (CH₂)_rC₃₋₆ cycloalkyl, Cl, F, Br, I, CN, NO₂, (CF₂)_rCF₃, (CH₂)_rOC₁₋₅ alkyl, OH, SH, C(O)OC₁₋₅ alkyl, (CH₂)_rSC₁₋₅ alkyl, (CH₂)_rNR^{7f}R^{7f}, and (CH₂)_rphenyl;

15 R^{7f}, at each occurrence, is selected from H, methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, hexyl, cyclopropyl, and phenyl; and

r is 0 or 1.

20

In another embodiment, the present invention provides novel compounds of formula (I), wherein:

25 R⁶, at each occurrence, is selected from C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, (CR'R')_rC₃₋₆ cycloalkyl, Cl, Br, I, F, NO₂, CN, (CR'R')_rNR^{6a}R^{6a}, (CR'R')_rOH, (CR'R')_rO(CR'R')_rR^{6d}, (CR'R')_rSH, (CR'R')_rC(O)H, (CR'R')_rS(CR'R')_rR^{6d}, (CR'R')_rC(O)OH, (CR'R')_rC(O)(CR'R')_rR^{6b}, (CR'R')_rC(O)NR^{6a}R^{6a}, (CR'R')_rNR^{6f}C(O)(CR'R')_rR^{6b}, (CR'R')_rC(O)O(CR'R')_rR^{6d}, (CR'R')_rNR^{6a}C(O)NR^{6a}R^{6a}, (CR'R')_rNR^{6a}C(S)NR^{6a}R^{6a}, (CR'R')_rOC(O)(CR'R')_rR^{6b}, (CR'R')_rS(O)_p(CR'R')_rR^{6b}, (CR'R')_rS(O)₂NR^{6a}R^{6a}, (CR'R')_rNR^{6f}S(O)₂(CR'R')_rR^{6b}, (CR'R')_rNR^{6f}S(O)₂NR^{6a}R^{6a}, C₁₋₆ haloalkyl, and

30

(CR'R')_rphenyl substituted with 0-3 R^{6e}, and a
 (CH₂)_{r-5-6} membered heterocyclic system containing 1-
 2 heteroatoms selected from N, O, and S, substituted
 with 0-2 R^{6e};

5

R^{6a}, at each occurrence, is independently selected from H,
 methyl, ethyl, propyl, i-propyl, butyl, i-butyl,
 t-butyl, pentyl, hexyl, cyclopropyl and phenyl;

10 R^{6b}, at each occurrence, is selected from methyl, ethyl,
 propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl,
 hexyl, cyclopropyl, and phenyl;

R^{6d}, at each occurrence, is selected from methyl, CF₃,
 15 ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl,
 pentyl, hexyl, cyclopropyl, and phenyl;

R^{6e}, at each occurrence, is selected from C₁₋₆ alkyl, C₂₋₈
 alkenyl, C₂₋₈ alkynyl, (CH₂)_rC₃₋₆ cycloalkyl, Cl, F,
 20 Br, I, CN, NO₂, (CF₂)_rCF₃, (CH₂)_rOC₁₋₅ alkyl, OH, SH,
 (CH₂)_rSC₁₋₅ alkyl, (CH₂)_rNR^{6f}R^{6f}, and (CH₂)_rphenyl;

R^{6f}, at each occurrence, is selected from H, methyl,
 ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl,
 25 pentyl, hexyl, cyclopropyl, and phenyl;

R⁷ is selected from methyl, ethyl, propyl, i-propyl,
 butyl, i-butyl, s-butyl, t-butyl, pentyl, hexyl,
 (CR'R')_rC₃₋₆ cycloalkyl, Cl, Br, I, F, NO₂, CN,
 30 (CR'R')_rNR^{7a}R^{7a}, (CR'R')_rOH, (CR'R')_rO(CH)_rR^{7d},
 (CR'R')_rSH, (CR'R')_rC(O)H, (CR'R')_rS(CR'R')_rR^{7d},
 (CR'R')_rC(O)OH, (CR'R')_rC(O)(CR'R')_rR^{7b},
 (CR'R')_rC(O)NR^{7a}R^{7a}, (CR'R')_rNR^{7f}C(O)(CR'R')_rR^{7b},
 (CR'R')_rC(O)O(CR'R')_rR^{7d}, (CR'R')_rOC(O)(CR'R')_rR^{7b},
 35 (CR'R')_rNR^{7a}C(O)NR^{7a}R^{7a}, (CR'R')_rNR^{7a}C(O)O(CR'R')_rR^{7d},

$(CR'R')_rS(O)_p(CR'R')_rR^{7b}$, $(CR'R')_rS(O)_2NR^{7a}R^{7a}$,
 $(CR'R')_rNR^{7f}S(O)_2(CR'R')_rR^{7b}$, C₁₋₆ haloalkyl,
 adamantyl, and $(CR'R')_r$ phenyl substituted with 0-3
 R^{7e};

5

R^{7a}, at each occurrence, is selected from H, methyl,
 ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl,
 pentyl, hexyl,, prop-2-enyl, 2-methyl-2-propenyl,
 cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,
 10 CH₂cyclopropyl, and benzyl;

R^{7b}, at each occurrence, is selected from methyl, ethyl,
 propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl,
 hexyl, cyclopropyl, cyclopentyl, CH₂-cyclopentyl,
 15 cyclohexyl, CH₂-cyclohexyl, CF₃, pyrrolidinyl,
 morpholinyl, piperizenyl substituted with 0-1 R^{7e},
 and azetidiny;

R^{7d}, at each occurrence, is selected from methyl, CF₃,
 20 CF₂CF₃, CHF₂, CH₂F, ethyl, propyl, i-propyl, butyl,
 i-butyl, t-butyl, pentyl, hexyl, and cyclopropyl;

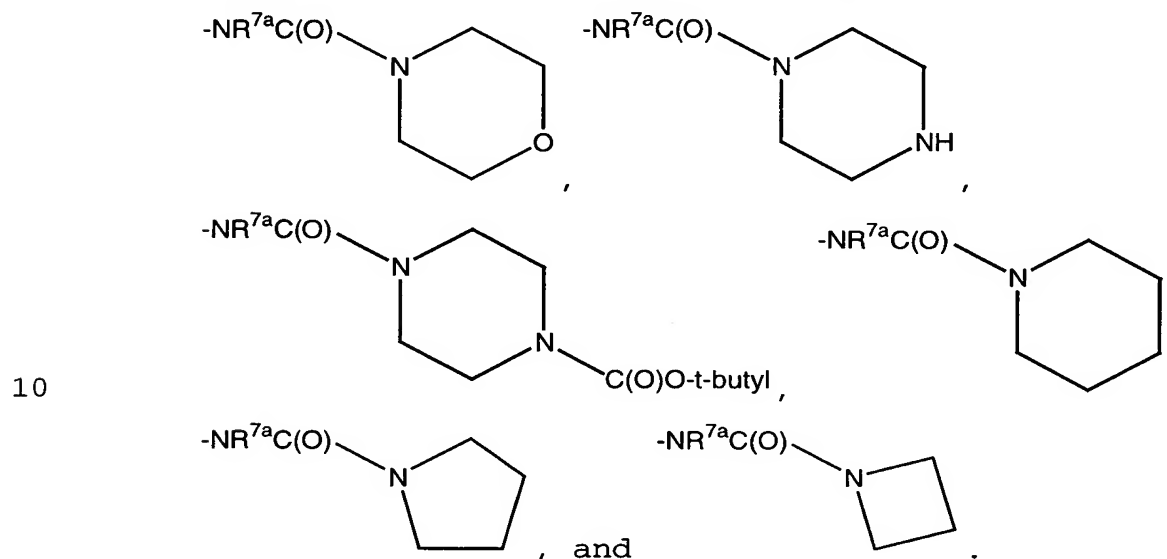
R^{7e}, at each occurrence, is selected from C₁₋₆ alkyl, C₂₋₈
 alkenyl, C₂₋₈ alkynyl, (CH₂)_rC₃₋₆ cycloalkyl, Cl, F,
 25 Br, I, CN, NO₂, (CF₂)_rCF₃, (CH₂)_rOC₁₋₅ alkyl, OH, SH,
 C(O)OC₁₋₅ alkyl, (CH₂)_rSC₁₋₅ alkyl, (CH₂)_rNR^{7f}R^{7f}, and
 (CH₂)_rphenyl;

R^{7f}, at each occurrence, is selected from H, methyl,
 30 ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl,
 pentyl, hexyl, cyclopropyl, and phenyl; and

r is 0 or 1.

In another embodiment, the present invention provides novel compounds of formula (I), wherein:

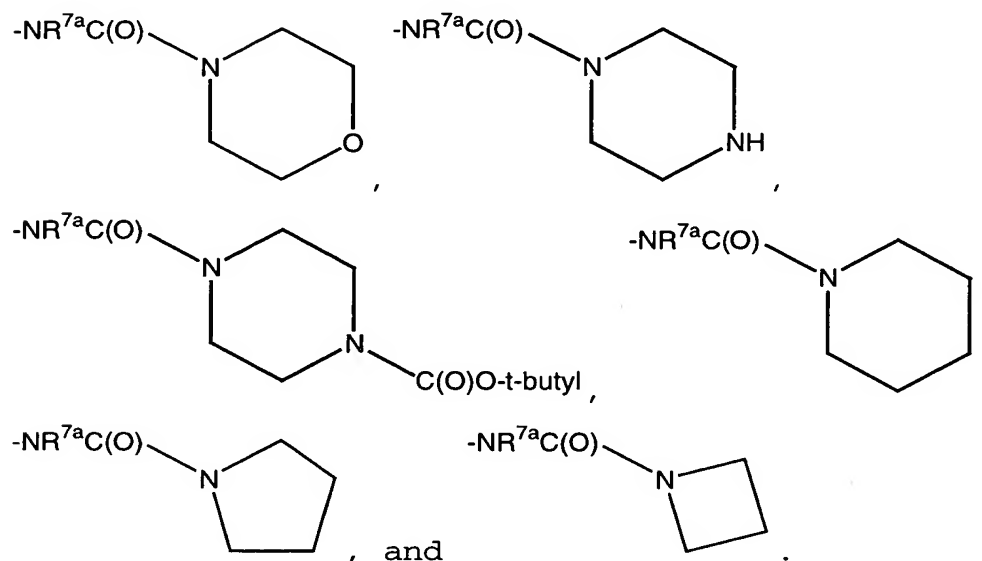
5 R^7 is selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, s-butyl, pentyl, hexyl, Cl, Br, I, F, CN, NO_2 , $\text{NR}^{7a}\text{R}^{7a}$, $\text{NHC}(\text{O})\text{NHR}^{7a}$, $\text{NR}^{7a}\text{C}(\text{O})\text{R}^{7b}$, $\text{NR}^{7a}\text{C}(\text{O})\text{OR}^{7d}$, CF_3 , CF_2CF_3 , CHF_2 , CH_2F , OCF_3 , $\text{C}(\text{O})\text{R}^{7b}$, $\text{C}(\text{O})\text{OR}^{7d}$, $\text{NR}^{7f}\text{C}(\text{O})\text{NR}^{7a}\text{R}^{7a}$, $\text{NHS}(\text{O})_2\text{R}^{7b}$,



In another embodiment, the present invention provides novel compounds of formula (I), wherein:


15 R^7 is selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, s-butyl, pentyl, hexyl, Cl, Br, I, F, CN, NO_2 , $\text{NR}^{7a}\text{R}^{7a}$, $\text{NHC}(\text{O})\text{NHR}^{7a}$, $\text{NR}^{7a}\text{C}(\text{O})\text{R}^{7b}$, $\text{NR}^{7a}\text{C}(\text{O})\text{OR}^{7d}$, CF_3 , CF_2CF_3 , CHF_2 , CH_2F , OCF_3 , $\text{C}(\text{O})\text{R}^{7b}$,

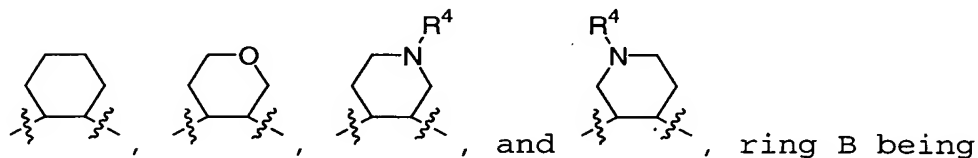
20 $\text{C}(\text{O})\text{OR}^{7d}$, $\text{NR}^{7f}\text{C}(\text{O})\text{NR}^{7a}\text{R}^{7a}$, $\text{NHS}(\text{O})_2\text{R}^{7b}$, adamantyl,



5

In another embodiment, the present invention provides novel compounds of formula (I), wherein:

ring B is selected from , , , and



10 optionally substituted with 0-1 R^5 ;

Z is selected from a bond, $-NR^8C(O)-$, $-C(O)NH-$, and $-NHC(O)NH-$;

15 R^1 is selected from a C_{6-10} aryl group substituted with 0-3 R^6 wherein the aryl group is selected from phenyl and naphthyl, and a 5-10 membered heteroaryl system containing 1-4 heteroatoms selected from N and O, substituted with 0-3 R^6 wherein the

20 heteroaryl system is selected from indolyl and pyridinyl;

R^2 is phenyl substituted with 0-2 R^7 ;

R⁴ is selected from H, methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, hexyl, and (CH₂)_r C(O)R^{4b};

5

R⁶ is selected from methyl, ethyl, propyl, i-propyl, butyl, F, Cl, Br, I, NO₂, CN, O(CH₂)_rR^{6d}, C(O)H, C(O)R^{6d}, C(O)OH, SR^{6d}, NR^{6a}R^{6a}, NC(O)R^{6b}, OC(O)R^{6b}, S(O)_pR^{6b}, (CHR')_rS(O)₂NR^{6a}R^{6a}, and CF₃;

10

R^{6a} is H, methyl, or ethyl;

R^{6b} is H, methyl, ethyl, propyl, i-propyl or butyl;

15 R^{6d} is methyl, phenyl, CF₃, and (CH₂)-phenyl; and

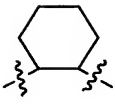
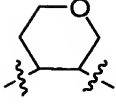
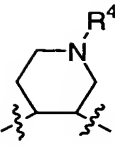
r is 0 or 1.

20 In another embodiment, the present invention provides novel compounds of formula (I), wherein:

R¹ is selected from a C₆₋₁₀ aryl group substituted with 0-3 R⁶ wherein the aryl group is selected from phenyl and naphthyl, and a 5-10 membered heteroaryl system containing 1-4 heteroatoms selected from N and O, substituted with 0-3 R⁶ wherein the heteroaryl system is selected from indolyl, pyridinyl, pyrimidinyl, pyrido[2,3-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, imidazolyl, and pyrrolyl.

30

In another embodiment, the present invention provides novel compounds of formula (I), wherein:

ring B is selected from , , and , ring B being substituted with 0-1 R⁵;

R¹ is selected from a C₆₋₁₀ aryl group substituted with
 5 0-3 R⁶ wherein the aryl group is selected from phenyl, and a 5-10 membered heteroaryl system containing 1-4 heteroatoms selected from N and O, substituted with 0-3 R⁶ wherein the heteroaryl system is selected from indolyl and pyridinyl;

10 R⁴ is selected from H, methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, hexyl, allyl and (CH₂)_r C(O)R^{4b};

15 R⁵ is selected from H, OH, OCH₃, and NR^{5a}R^{5a};

R^{5a} is selected from H, methyl, ethyl, propyl, i-propyl, butyl, s-butyl, i-butyl, t-butyl, pentyl, hexyl, allyl, propargyl, cyclopropyl, cyclopropylmethyl,
 20 acetyl, methanesulfonyl, -C(O)CF₃, C(=N)NH₂, benzyl, and -C(O)O-t-butyl;

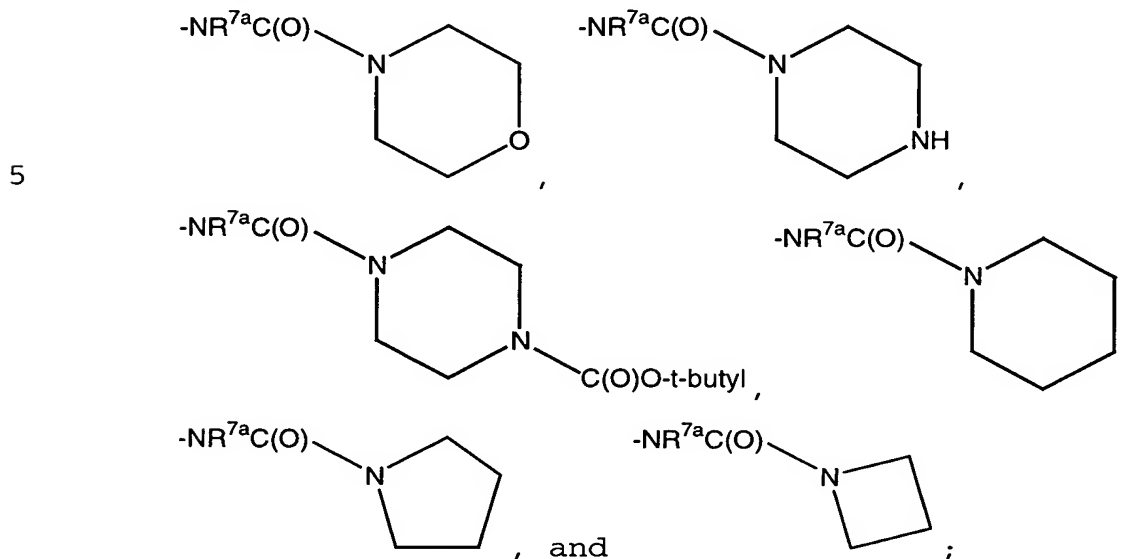
R⁶ is selected from methyl, ethyl, propyl, i-propyl, butyl, vinyl, F, Cl, Br, I, CN, NR^{6a}R^{6a}, C(O)H,
 25 C(O)OH, C(O)R^{6b}, SR^{6d}, S(O)_pR^{6d}, S(O)₂NR^{6a}R^{6a}, CF₃, and CH₂OH;

R^{6b} is H, methyl, ethyl, propyl, i-propyl or butyl;

30 R^{6d} is methyl;

R⁷ is selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, s-butyl, pentyl, hexyl, Cl, Br, I,

F, CN, NO₂, NR^{7a}R^{7a}, NHC(O)NHR^{7a}, NR^{7a}C(O)R^{7b},
 NR^{7a}C(O)OR^{7d}, CF₃, CF₂CF₃, CHF₂, CH₂F, OCF₃, OCF₂CF₃,
 OCHF₂, and OCH₂F, C(O)OR^{7d}, C(O)R^{7b}, NR^{7f}C(O)NR^{7a}R^{7a},
 NHS(O)₂R^{7b},

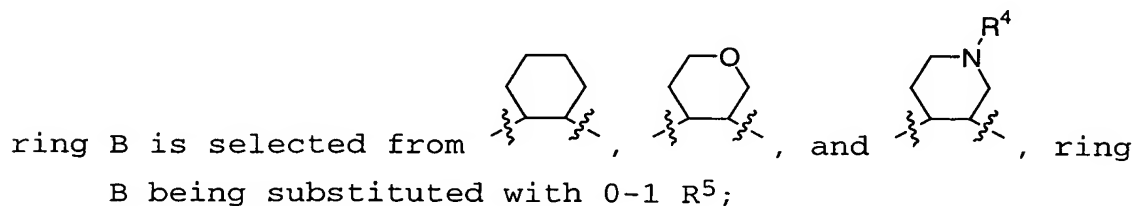


10 R^{7a} is selected from H, methyl, ethyl, propyl, i-propyl,
 butyl, i-butyl, t-butyl, pentyl, neo-pentyl,
 cyclopropyl, cyclobutyl, cyclopentyl, and
 cyclohexyl;

15 R^{7b} is selected from cyclohexyl and CF₃; and

R^{7d} is selected from methyl, ethyl, propyl, i-propyl,
 butyl, i-butyl, and t-butyl.

20 In another embodiment, the present invention
 provides novel compounds of formula (I), wherein:



R¹ is selected from a C₆₋₁₀ aryl group substituted with
 0-3 R⁶ wherein the aryl group is selected from
 phenyl, and a 5-10 membered heteroaryl system
 containing 1-4 heteroatoms selected from N and O,
 5 substituted with 0-3 R⁶ wherein the heteroaryl
 system is selected from indolyl and pyridinyl;

R⁴ is selected from H, methyl, ethyl, propyl, i-propyl,
 butyl, i-butyl, t-butyl, pentyl, hexyl, allyl and
 10 (CH₂)_r C(O)R^{4b};

R⁵ is selected from H, OH, OCH₃, N(→O)R^{5a}R^{5a}, N₃,
 NR^{5a}C(O)R^{5b}, NR^{5a}C(O)H, NR^{5a}C(O)OR^{5d}, NR^{5a}C(O)NR^{5a}R^{5a},
 and NR^{5a}R^{5a}, and a (CH₂)_r-5-6 membered heterocyclic
 15 system containing 1-2 heteroatoms selected from N,
 O, and S, substituted with 0-2 R^{5e}, wherein the
 heterocyclic system is selected from pyrrolidinyl,
 piperidinyl, pyrrolidin-2-one, and isothiazolidine
 1,1-dioxide;

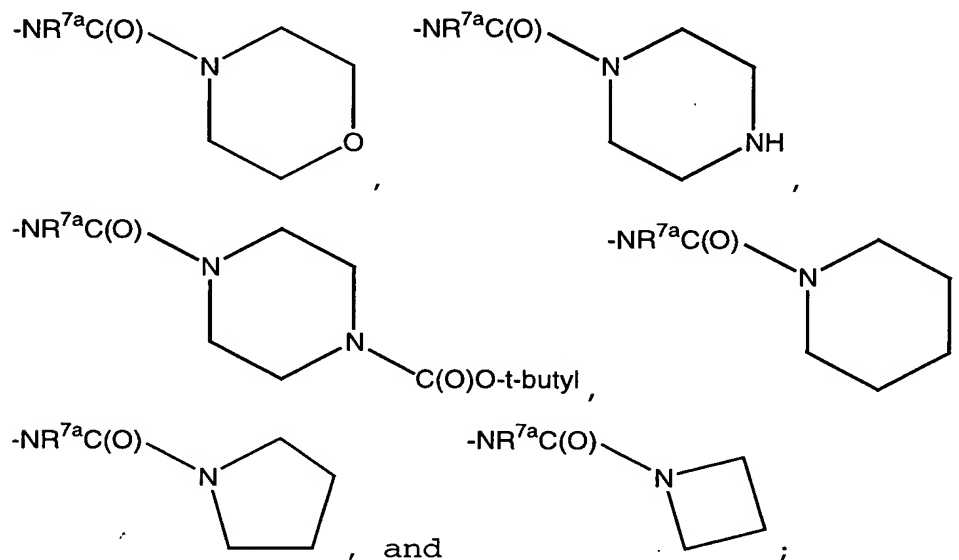
20 R^{5a} is selected from H, methyl substituted with 0-1 R^{5g},
 ethyl substituted with 0-1 R^{5e}, propyl, i-propyl,
 butyl, s-butyl, i-butyl, t-butyl, pentyl, hexyl,
 allyl, propargyl, cyclopropyl, cyclopropylmethyl,
 25 phenyl, benzyl, pyridin-3-yl, thiazolyl,;

R⁶ is selected from methyl, ethyl, propyl, i-propyl,
 butyl, vinyl, F, Cl, Br, I, CN, NR^{6a}R^{6a}, C(O)H,
 C(O)OH, C(O)R^{6b}, SR^{6d}, S(O)_pR^{6d}, S(O)₂NR^{6a}R^{6a}, CF₃,
 30 and CH₂OH;

R^{6b} is H, methyl, ethyl, propyl, i-propyl or butyl;

R^{6d} is methyl;

R^7 is selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, s-butyl, t-butyl, pentyl, hexyl, phenyl, adamantyl, benzyl, Cl, Br, I, F, CN, NO₂,
 5 $NR^{7a}R^{7a}$, OR^{7d} , $NHC(O)NHR^{7a}$, $NR^{7a}C(O)R^{7b}$, $NR^{7a}C(O)OR^{7d}$,
 CF_3 , CF_2CF_3 , CHF_2 , CH_2F , OCF_3 , OCF_2CF_3 , $OCHF_2$, and
 OCH_2F , $C(O)OR^{7d}$, $C(O)R^{7b}$, $NR^{7f}C(O)NR^{7a}R^{7a}$, $NHS(O)_2R^{7b}$,



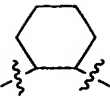
10

R^{7a} is selected from H, methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, neo-pentyl, cyclopropyl, cyclobutyl, cyclopentyl, and
 15 cyclohexyl;

R^{7b} is selected from cyclohexyl and CF_3 ; and

R^{7d} is selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, and t-butyl.
 20

In another embodiment, the present invention provides novel compounds of formula (I), wherein:

ring B is selected from , ring B being substituted with 0-1 R⁵;

R¹ is selected from a C₆₋₁₀ aryl group substituted with
 5 0-3 R⁶ wherein the aryl group is phenyl, and a 5-10
 membered heteroaryl system containing 1 heteroatoms
 selected from N and O, substituted with 0-3 R⁶
 wherein the heteroaryl system is indolyl;

10 R⁵ is selected from H, OH, OCH₃, and NR^{5a}R^{5a};

R^{5a} is selected from H, methyl, ethyl, propyl, i-propyl,
 butyl, s-butyl, i-butyl, t-butyl, pentyl, hexyl,
 allyl, propargyl, cyclopropyl, cyclopropylmethyl,
 15 acetyl, methysulfonyl, -C(O)CF₃, C(=N)NH₂, benzyl,
 and -C(O)O-t-butyl;

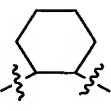
R⁶ is selected from methyl, ethyl, propyl, i-propyl, Cl,
 Br, CN, C(O)CH₃, C(O)OH, OCH₃, NR^{6a}R^{6a}, SCH₃,
 20 S(O)₂NR^{6a}R^{6a}, and CF₃;

R^{6a} is H, methyl, ethyl, propyl, i-propyl, butyl,
 propargyl, cyclopropyl, allyl;

25 R⁷ is selected from Cl, Br, CN, NR^{7a}R^{7a}, CF₃, CF₂CF₃, CHF₂,
 CH₂F, OCF₃, OCF₂CF₃, OCHF₂, and OCH₂F; and

R^{7a} is selected from H, methyl, ethyl, propyl, i-propyl,
 butyl, i-butyl, t-butyl, pentyl, neo-pentyl,
 30 cyclopropyl, cyclobutyl, cyclopentyl, and
 cyclohexyl.

In another embodiment, the present invention
 provides novel compounds of formula (I), wherein:

ring B is selected from , ring B being substituted with 0-1 R⁵;

5 R¹ is selected from a C₆₋₁₀ aryl group substituted with 0-3 R⁶ wherein the aryl group is phenyl;

R⁶ is selected from methyl, ethyl, propyl, i-propyl, F, Cl, Br, CN, SCH₃, and CF₃;

10

R⁷ is selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, s-butyl, t-butyl, pentyl, hexyl, phenyl, adamantyl, benzyl, Cl, Br, I, F, CN, NO₂, NR^{7a}R^{7a}, OR^{7d}, NHC(O)NHR^{7a}, NR^{7a}C(O)R^{7b}, NR^{7a}C(O)OR^{7d},
 15 CF₃, CF₂CF₃, CHF₂, CH₂F, OCF₃, OCF₂CF₃, OCHF₂, and OCH₂F, C(O)OR^{7d}, C(O)R^{7b}, and NR^{7f}C(O)NR^{7a}R^{7a};

R^{7a} is selected from H, methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, neo-pentyl,
 20 cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

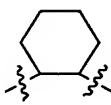
In another embodiment, the present invention provides novel compounds of formula (I), wherein:

25

E is selected from -CH₂-NH-, -C(O)-NH- and -SO₂-CH₂-.

In another embodiment, the present invention provides novel compounds of formula (I), wherein:

30

B is , ring B being substituted with 0-1 R⁵; and

R⁵ is selected from H and NR^{5a}R^{5a};

R^{5a} is selected from H, methyl, ethyl, propyl, i-propyl,
butyl, s-butyl, i-butyl, t-butyl, pentyl, hexyl,
5 propargyl, allyl, cyclopropylmethyl, cyclopropyl,
and phenyl.

In another embodiment, the present invention
provides novel compounds of formula (I), wherein:

10 Z is selected from a bond, -NR⁸C(O)-, -C(O)NH-, and
-NHC(O)NH-.

In another embodiment, the present invention
15 provides novel compounds of formula (I), wherein:

R⁶ is selected from methyl, ethyl, propyl, i-propyl,
butyl, vinyl, F, Cl, Br, I, C(O)H, C(O)R^{6b}, SR^{6d},
S(O)_pR^{6d}, CF₃, and CH₂OH;

20 R^{6b} is H, methyl, ethyl, propyl, i-propyl or butyl;

R^{6d} is methyl;

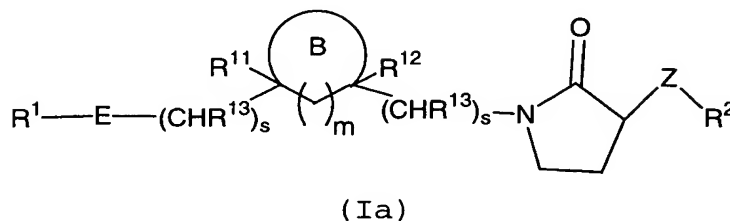
25 R⁷ is selected from Cl, Br, NR^{7a}R^{7a}, NR^{7a}C(O)OR^{7d},
NHC(O)NHR^{7a}, OCF₃, and CF₃;

R^{7a} is selected from H, methyl, ethyl, propyl, i-propyl,
butyl, i-butyl, t-butyl, pentyl, neo-pentyl,
30 cyclopropyl, cyclobutyl, cyclopentyl, and
cyclohexyl;

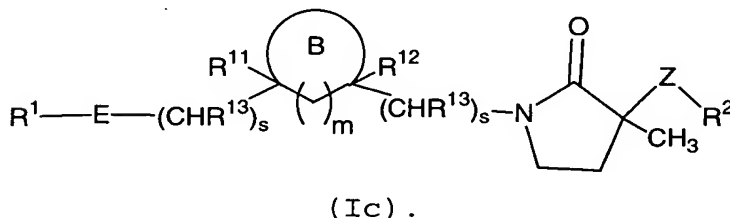
R^{7d} is selected from methyl, ethyl, propyl, i-propyl,
butyl, i-butyl, and t-butyl.

35

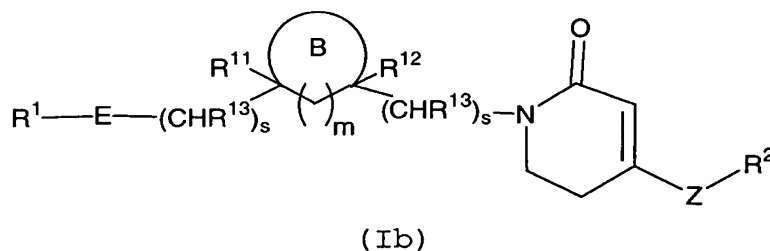
In another embodiment, the present invention provides novel compounds of formula (Ia) or (Ic), wherein:



or



In another embodiment, the present invention provides novel compounds of formula (Ib), wherein:



In another embodiment, the present invention provides novel compounds of formula (I), wherein the compound is selected from the compounds of the examples.

20

In another embodiment, the present invention is directed to a pharmaceutical composition, comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Formula (I).

25

In another embodiment, the present invention is directed to a method for modulation of chemokine or

chemokine receptor activity comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I).

5 In another embodiment, the present invention is directed to a method for modulation of CCR-2 receptor activity comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I).

10

 In another embodiment, the present invention is directed to a method for modulation of MCP-1, MCP-2, MCP-3 and MCP-4, and MCP-5 activity that is mediated by the CCR2 receptor comprising administering to a patient in
15 need thereof a therapeutically effective amount of a compound of Formula (I).

 In another embodiment, the present invention is directed to a method for modulation of MCP-1 activity
20 comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I).

 In another embodiment, the present invention is
25 directed to a method for treating disorders, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I), said disorders being selected from osteoarthritis, aneurism, fever, cardiovascular effects, Crohn's disease, congestive heart failure, autoimmune diseases, HIV-
30 infection, HIV-associated dementia, psoriasis, idiopathic pulmonary fibrosis, transplant arteriosclerosis, physically- or chemically-induced brain trauma, inflammatory bowel disease, alveolitis, colitis, systemic
35 lupus erythematosus, nephrotoxic serum nephritis, glomerular nephritis, asthma, multiple sclerosis,

atherosclerosis, rheumatoid arthritis, restinosis, organ transplantation, and cancer.

In another embodiment, the present invention is
5 directed to a method for treating disorders, of Formula
(I), wherein said disorders being selected from
psoriasis, idiopathic pulmonary fibrosis, transplant
arteriosclerosis, physically- or chemically-induced brain
trauma, inflammatory bowel disease, alveolitis, colitis,
10 systemic lupus erythematosus, nephrotoxic serum
nephritis, glomerularnephritis, asthma, multiple
sclerosis, atherosclerosis, and rheumatoid arthritis,
restinosis, organ transplantation, and cancer.

15 In another embodiment, the present invention is
directed to a method for treating disorders, of Formula
(I), wherein said disorders being selected from
alveolitis, colitis, systemic lupus erythematosus,
nephrotoxic serum nephritis, glomerularnephritis, asthma,
20 multiple sclerosis, atherosclerosis, and rheumatoid
arthritis, restinosis, organ transplantation, and cancer.

In another embodiment, the present invention is
directed to a method for treating disorders, of Formula
25 (I), wherein said disorders being selected from asthma,
multiple sclerosis, atherosclerosis, and rheumatoid
arthritis.

In another embodiment, the present invention is
30 directed to a method for treating disorders, of Formula
(I), wherein said disorders being selected from
restinosis, organ transplantation, and cancer.

In another embodiment, the present invention is directed to a method for treating rheumatoid arthritis, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I).

In another embodiment, the present invention is directed to a method for treating multiple sclerosis, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I).

In another embodiment, the present invention is directed to a method for treating atherosclerosis, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I).

In another embodiment, the present invention is directed to a method for treating asthma, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I).

In another embodiment, the present invention is directed to a method for treating restinosis, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I).

In another embodiment, the present invention is directed to a method for treating organ transplantation, comprising administering to a patient in need thereof a

therapeutically effective amount of a compound of Formula (I).

5 In another embodiment, the present invention is directed to a method for treating cancer, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I).

10 In another embodiment, the present invention is directed to a method for treating inflammatory diseases, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I).

15 In another embodiment, the present invention is directed to a method for treating inflammatory diseases which are at least partially mediated by CCR-2, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I).

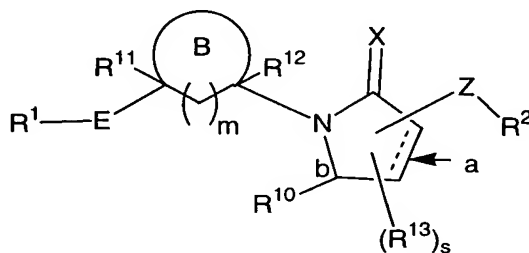
20 In another embodiment, the present invention is directed to a method for modulation of CCR2 activity comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I).

25 In another embodiment, the present invention is directed the use of a compound of Formula (I) in the preparation of a medicament for the treatment of osteoarthritis, aneurism, fever, cardiovascular effects, Crohn's disease, congestive heart failure, autoimmune

diseases, HIV-infection, HIV-associated dementia,
 psoriasis, idiopathic pulmonary fibrosis, transplant
 arteriosclerosis, physically- or chemically-induced brain
 trauma, inflammatory bowel disease, alveolitis, colitis,
 5 systemic lupus erythematosus, nephrotoxic serum
 nephritis, glomerularnephritis, asthma, multiple
 sclerosis, artherosclerosis, and rheumatoid arthritis.

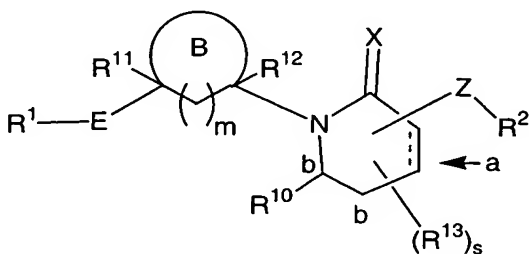
In another embodiment, the present invention is
 10 directed to a compound of formula (I) for use in therapy.

In another embodiment, the present invention is
 directed to a compound of formula (Ia)



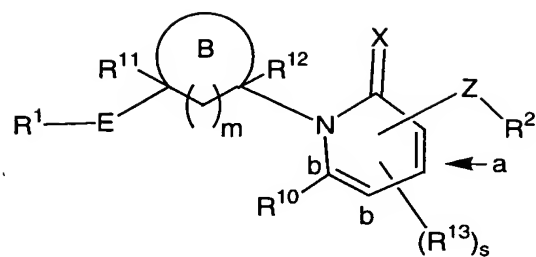
15 (Ia) .

In another embodiment, the present invention is
 directed to a compound of formula (Ib)



20 (Ib) .

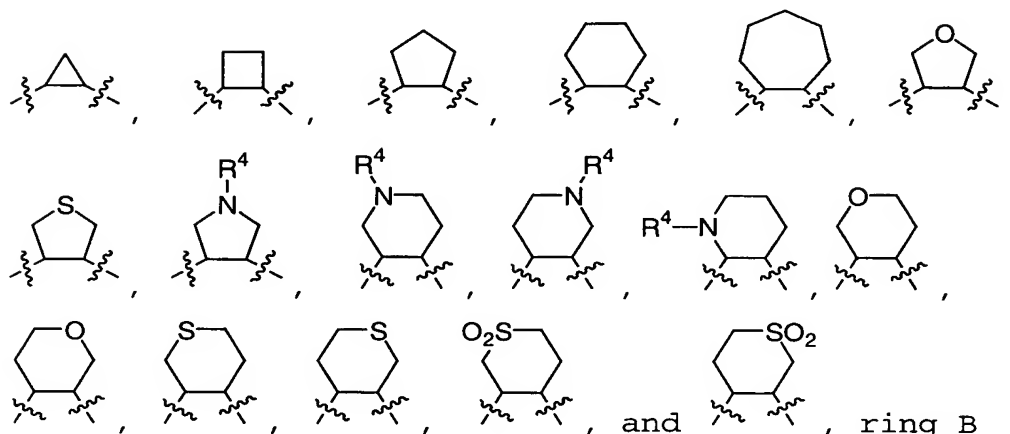
In another embodiment, the present invention is
 directed to a compound of formula (Ic)



(Ic).

In another embodiment, ring B is selected from

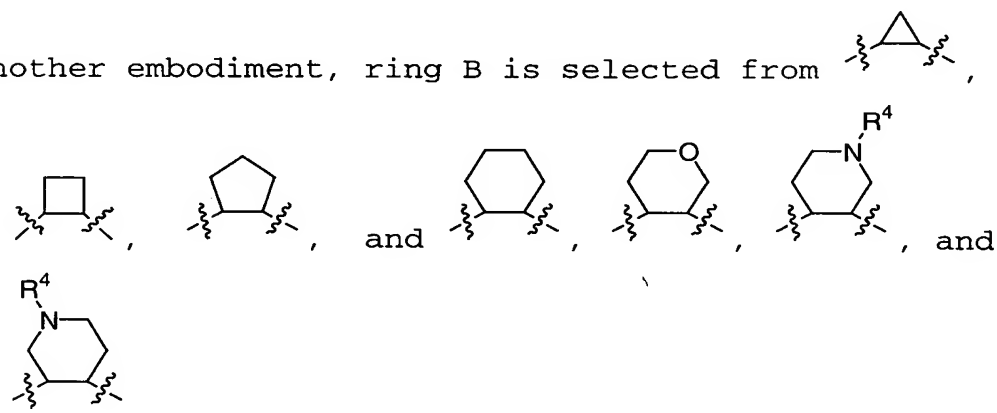
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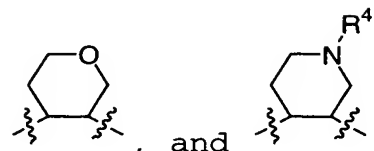
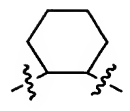
being optionally substituted with 0-1 R^5 .

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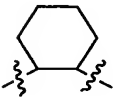
In another embodiment, ring B is selected from



In another embodiment, ring B is selected from



, and , ring B being substituted with 0-1 R^5 ;

5 In another embodiment, ring B is , ring B being substituted with 0-1 R^5 ;

In another embodiment, E is $-S(O)_pCH_2-$.

10 In another embodiment, E is $-C(O)NH-$.

In another embodiment, E is $-CH_2NH-$.

In another embodiment, Z is selected from a bond,
 15 $-NR^8C(O)-$, $-NR^8C(O)NH-$, $-NR^8SO_2-$, $-NR^8SO_2NH-$,
 $-C(O)NR^8-$, $-(CR^{15}R^{15})_1-$, $-CR^{14}=CR^{14}-$, $-CR^{15}R^{15}C(O)-$,
 $-C(O)CR^{15}R^{15}-$, $-O-CR^{14}R^{14}-$, $-CR^{14}R^{14}-O-$, $-O-$, $-NR^9-$,
 $-NR^9-CR^{14}R^{14}-$, $-CR^{14}R^{14}-NR^9-$, $-S(O)_p-$, $-S(O)_p-CR^{14}R^{14}-$,
 $-CR^{14}R^{14}-S(O)_p-$, and $-S(O)_p-NR^9-$.

20 In another embodiment, Z is selected from a bond,
 $-NR^8C(O)-$, $-NR^8C(O)NH-$, $-C(O)NR^8-$, $-(CR^{15}R^{15})_1-$,
 $-CR^{15}R^{15}C(O)-$, $-C(O)CR^{15}R^{15}-$, $-O-CR^{14}R^{14}-$, $-CR^{14}R^{14}-O-$,
 $-O-$, $-NR^9-$, $-NR^9-CR^{14}R^{14}-$, $-CR^{14}R^{14}-NR^9-$, $-S(O)_p-$,
 25 $-S(O)_p-CR^{14}R^{14}-$, and $-S(O)_p-NR^9-$.

In another embodiment, Z is selected from a bond,
 $-NR^8C(O)-$, $-NR^8C(O)NH-$, and $-C(O)NR^8-$.

In another embodiment, Z is selected from a bond,
 $-\text{NR}^8\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NH}-$, and $-\text{NHC}(\text{O})\text{NH}-$.

In another embodiment, Z is selected from $-\text{C}(\text{O})\text{NH}-$.

5

In another embodiment, Z is selected from a bond, and
 $-\text{NHC}(\text{O})-$;

In another embodiment, Z is a bond.

10

In another embodiment, R^4 is selected from H, C_{1-6} alkyl,
 C_{3-8} alkenyl, C_{3-8} alkynyl, $(\text{CRR})_q\text{OH}$, $(\text{CHR})_s\text{SH}$,
 $(\text{CRR})_t\text{OR}^{4d}$, $(\text{CHR})_t\text{SR}^{4d}$, $(\text{CHR})_t\text{NR}^{4a}\text{R}^{4a}$, $(\text{CHR})_q\text{C}(\text{O})\text{OH}$,
 $(\text{CHR})_r\text{C}(\text{O})\text{R}^{4b}$, $(\text{CHR})_r\text{C}(\text{O})\text{NR}^{4a}\text{R}^{4a}$, $(\text{CHR})_t\text{NR}^{4a}\text{C}(\text{O})\text{R}^{4b}$,
15 $(\text{CHR})_t\text{OC}(\text{O})\text{NR}^{4a}\text{R}^{4a}$, $(\text{CHR})_t\text{NR}^{4a}\text{C}(\text{O})\text{OR}^{4d}$,
 $(\text{CHR})_t\text{NR}^{4a}\text{C}(\text{O})\text{R}^{4b}$, $(\text{CHR})_r\text{C}(\text{O})\text{OR}^{4b}$, $(\text{CHR})_t\text{OC}(\text{O})\text{R}^{4b}$,
 $(\text{CHR})_r\text{S}(\text{O})_p\text{R}^{4b}$, $(\text{CHR})_r\text{S}(\text{O})_2\text{NR}^{4a}\text{R}^{4a}$, $(\text{CHR})_r\text{NR}^{4a}\text{S}(\text{O})_2\text{R}^{4b}$,
and

20 R, at each occurrence, is independently selected from H,
methyl, ethyl, propyl, allyl, propynyl, $(\text{CH}_2)_r\text{C}_{3-6}$
cycloalkyl, and $(\text{CH}_2)_r$ phenyl substituted with R^{6e} .

In another embodiment, R^4 is selected from H, methyl,
25 ethyl, propyl, i-propyl, butyl, i-butyl, allyl,
propynyl, $(\text{CRR})_q\text{OH}$, $(\text{CRR})_t\text{SH}$, $(\text{CRR})_t\text{OR}^{4d}$, $(\text{CRR})_t\text{SR}^{4d}$,
 $(\text{CRR})_t\text{NR}^{4a}\text{R}^{4a}$, $(\text{CRR})_q\text{C}(\text{O})\text{OH}$, $(\text{CRR})_r\text{C}(\text{O})\text{R}^{4b}$,
 $(\text{CRR})_r\text{C}(\text{O})\text{NR}^{4a}\text{R}^{4a}$, $(\text{CRR})_t\text{NR}^{4a}\text{C}(\text{O})\text{R}^{4b}$,
 $(\text{CRR})_t\text{OC}(\text{O})\text{NR}^{4a}\text{R}^{4a}$, $(\text{CRR})_t\text{NR}^{4a}\text{C}(\text{O})\text{OR}^{4d}$,
30 $(\text{CRR})_t\text{NR}^{4a}\text{C}(\text{O})\text{R}^{4b}$, $(\text{CRR})_r\text{C}(\text{O})\text{OR}^{4b}$, $(\text{CRR})_t\text{OC}(\text{O})\text{R}^{4b}$,
 $(\text{CRR})_r\text{S}(\text{O})_p\text{R}^{4b}$, $(\text{CRR})_r\text{S}(\text{O})_2\text{NR}^{4a}\text{R}^{4a}$, $(\text{CRR})_r\text{NR}^{4a}\text{S}(\text{O})_2\text{R}^{4b}$.

R^{4b} is selected from H, methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, and cyclopropyl; and

5 R^{4d} is selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, and cyclopropyl.

In another embodiment, R^4 is selected from H, methyl, ethyl, propyl, i-propyl, butyl, i-butyl, allyl,
10 propynyl, $(CH_2)_rC(O)R^{4b}$.

In another embodiment, R^5 , at each occurrence, is independently selected from H, C_{1-6} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, $(CRR)_rOH$, $(CRR)_rSH$, $(CRR)_rOR^{5d}$,
15 $(CRR)_rSR^{5d}$, $(CRR)_rNR^{5a}R^{5a}$, $(CRR)_rN(O)R^{5a}R^{5a}$, N_3 , $(CRR)_rC(O)OH$, $(CRR)_rC(O)R^{5b}$, $(CRR)_rC(O)NR^{5a}R^{5a}$, $(CRR)_rNR^{5a}C(O)R^{5b}$, $(CRR)_rNR^{5a}C(O)OR^{5d}$, $(CRR)_rOC(O)NR^{5a}R^{5a}$, $(CHR)_rNR^{5a}C(O)NR^{5a}R^{5a}$, $(CRR)_rNR^{5a}C(O)H$, $(CRR)_rC(O)OR^{5b}$, $(CRR)_rOC(O)R^{5b}$,
20 $(CRR)_rS(O)_pR^{5b}$, $(CRR)_rS(O)_2NR^{5a}R^{5a}$, $(CRR)_rNR^{5a}S(O)_2R^{5b}$, and C_{1-6} haloalkyl.

In another embodiment, R^5 is selected from H, OH, OCH_3 , $N(\rightarrow O)R^{5a}R^{5a}$, N_3 , $NR^{5a}C(O)R^{5b}$, $NR^{5a}C(O)H$, $NR^{5a}C(O)OR^{5d}$,
25 $NR^{5a}C(O)NR^{5a}R^{5a}$, and $NR^{5a}R^{5a}$, and a $(CH_2)_{r-5-6}$ membered heterocyclic system containing 1-2 heteroatoms selected from N, O, and S, substituted with 0-2 R^{5e} , wherein the heterocyclic system is selected from pyrrolidinyl, piperidinyl, pyrrolidin-
30 2-one, and isothiazolidine 1,1-dioxide;

R^{5a} is selected from H, methyl substituted with 0-1 R^{5g} , ethyl substituted with 0-1 R^{5e} , propyl, i-propyl,

butyl, s-butyl, i-butyl, t-butyl, pentyl, hexyl, allyl, propargyl, cyclopropyl, cyclopropylmethyl, phenyl, benzyl, pyridin-3-yl, thiazolyl.

- 5 In another embodiment, R^5 is selected from H, $N(\rightarrow O)R^{5a}R^{5a}$, N_3 , $NR^{5a}C(O)R^{5b}$, $NR^{5a}C(O)H$, $NR^{5a}C(O)OR^{5d}$, $NR^{5a}C(O)NR^{5a}R^{5a}$, and $NR^{5a}R^{5a}$, and a $(CH_2)_r$ -5-6 membered heterocyclic system containing 1-2 heteroatoms selected from N, O, and S, substituted with 0-2 R^{5e} , wherein the heterocyclic system is selected from pyrrolidinyl, piperidinyl, pyrrolidin-2-one, and isothiazolidine 1,1-dioxide.

- 15 In another embodiment, R^5 , at each occurrence, is independently selected from H, C_{1-6} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, $(CH_2)_rOH$, $(CH_2)_rSH$, $(CH_2)_rOR^{5d}$, $(CH_2)_rSR^{5d}$, $(CH_2)_rNR^{5a}R^{5a}$, $(CH_2)_rN(O)R^{5a}R^{5a}$, N_3 , $(CH_2)_rC(O)OH$, $(CH_2)_rC(O)R^{5b}$, $(CH_2)_rC(O)NR^{5a}R^{5a}$, $(CH_2)_rNR^{5a}C(O)R^{5b}$, $(CH_2)_rNR^{5a}C(O)OR^{5d}$, $(CH_2)_rOC(O)NR^{5a}R^{5a}$, $(CHR)_rNR^{5a}C(O)NR^{5a}R^{5a}$, $(CH_2)_rNR^{5a}C(O)H$, $(CH_2)_rC(O)OR^{5b}$, $(CH_2)_rOC(O)R^{5b}$, $(CH_2)_rS(O)_pR^{5b}$, $(CH_2)_rS(O)_2NR^{5a}R^{5a}$, $(CH_2)_rNR^{5a}S(O)_2R^{5b}$, and C_{1-6} haloalkyl.

- 25 In another embodiment, R^5 , at each occurrence, is independently selected from H, methyl, ethyl, propyl, i-propyl, butyl, i-butyl, allyl, propynyl, $(CH_2)_rOH$, $(CH_2)_rOR^{5d}$, $(CH_2)_rNR^{5a}R^{5a}$, $(CH_2)_rC(O)OH$, $(CH_2)_rC(O)R^{5b}$, $(CH_2)_rC(O)NR^{5a}R^{5a}$, $(CH_2)_rNR^{5a}C(O)R^{5b}$, $(CH_2)_rOC(O)NR^{5a}R^{5a}$, $(CH_2)_rNR^{5a}C(O)OR^{5d}$, $(CH_2)_rNR^{5a}C(O)R^{5b}$, $(CH_2)_rC(O)OR^{5b}$, $(CH_2)_rOC(O)R^{5b}$, $(CH_2)_rNR^{5a}S(O)_2R^{5b}$, and C_{1-6} haloalkyl; and

- R^{5a} , at each occurrence, is independently selected from H, methyl, ethyl, propyl, i-propyl, butyl, i-butyl, pentyl, hexyl, cyclopropyl, and cyclobutyl.
- 5 In another embodiment, R^5 , at each occurrence, is independently selected from H, OH, OR^{5d} , $(CH_2)_rNR^{5a}R^{5a}$, $(CH_2)_rNR^{5a}C(O)R^{5b}$, and $(CH_2)_rNR^{5a}C(O)OR^{5d}$.
- 10 In another embodiment, R^1 is selected from phenyl substituted with 0-2 R^6 , naphthyl substituted with 0-2 R^6 , and a 5-10 membered heteroaryl system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^6 wherein the heteroaryl
- 15 is selected from indolyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalonyl, cinnolinyl, furanyl, imidazolyl, indazolyl, indolyl,
- 20 isoquinolinyl isothiazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyridinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, thiazolyl, thienyl, and tetrazolyl.
- 25 In another embodiment, R^1 is selected from a C_{6-10} aryl group substituted with 0-3 R^6 wherein the aryl group is selected from phenyl and naphthyl, and a 5-10 membered heteroaryl system containing 1-4 heteroatoms selected from N and O, substituted with
- 30 0-3 R^6 wherein the heteroaryl system is selected from furanyl, indolyl, benzothiazolyl, and benzotriazolyl.

In another embodiment, R¹ is selected from phenyl substituted with 0-2 R⁶, naphthyl substituted with 0-2 R⁶, and a 5-10 membered heteroaryl system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R⁶ wherein the heteroaryl is selected from indolyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzoxazolyl, benzthiazolyl, benzo[b]thiophene, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalonyl, cinnolinyl, furanyl, imidazolyl, indazolyl, indolyl, isoquinolinyl, isothiazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrido[2,3-d]pyrimidinyl, pyrimido[5,4-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, pyridinyl, pyrimidinyl, pyrrolyl, pyrrolo[2,1-f][1,2,4]triazine, quinazolinyl, quinolinyl, thiazolyl, thienyl, and tetrazolyl.

In another embodiment, R¹ is selected from a C₆₋₁₀ aryl group substituted with 0-3 R⁶ wherein the aryl group is selected from phenyl and naphthyl, and a 5-10 membered heteroaryl system containing 1-4 heteroatoms selected from N and O, substituted with 0-3 R⁶ wherein the heteroaryl system is selected from indolyl, pyridinyl, pyrimidinyl, pyrido[2,3-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, imidazolyl, and pyrrolyl.

In another embodiment, R¹ is selected from a C₆₋₁₀ aryl group substituted with 0-3 R⁶ wherein the aryl group is selected from phenyl, and a 5-10 membered heteroaryl system containing 1-4 heteroatoms selected from N and O, substituted with 0-3 R⁶

wherein the heteroaryl system is selected from indolyl and pyridinyl.

In another embodiment, R¹ is selected from a C₆₋₁₀ aryl group substituted with 0-3 R⁶ wherein the aryl group is phenyl.

In another embodiment, R² is selected from phenyl substituted with 0-2 R⁷, and a 5-10 membered heteroaryl system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R⁷ wherein the heteroaryl is selected from benzimidazolyl, benzofuranyl, benzothiofuranyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalonyl, cinnolinyl, furanyl, imidazolyl, indazolyl, indolyl, isoquinolinyl isothiazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyridinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, thiazolyl, thienyl, and tetrazolyl.

In another embodiment, R² is selected from phenyl substituted with 0-2 R⁷.

In another embodiment, R² is selected from phenyl substituted with 0-2 R⁷, and a 5-10 membered heteroaryl system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R⁷ wherein the heteroaryl is selected from indolyl, naphthalenyl, phthalazinyl, cinnolinyl, quinolinyl, isoquinolinyl, indazolyl, and quinazolinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl,

benzoxazolyl, benzthiazolyl, benzisoxazolyl, and
benzisothiazolyl.

In another embodiment, R^2 is selected from phenyl
5 substituted with 0-2 R^7 , and a 5-10 membered
heteroaryl system containing 1-4 heteroatoms
selected from N, O, and S, substituted with 0-3 R^7
wherein the heteroaryl is selected from indolyl,
benzimidazolyl, benzofuranyl, benzothiofuranyl,
10 benzoxazolyl, benzthiazolyl, benzo[b]thiophene,
benztriazolyl, benztetrazolyl, benzisoxazolyl,
benzisothiazolyl, benzimidazolyl, cinnolyl,
furanyl, imidazolyl, indazolyl, indolyl,
isoquinolyl, isothiazolyl, isoxazolyl, oxazolyl,
15 phthalazinyl, pyrazinyl, pyrazolyl, pyridazinyl,
pyridyl, pyrido[2,3-d]pyrimidinyl, thieno[3,2-
d]pyrimidinyl, pyridinyl, pyrimidinyl, pyrrolyl,
pyrrolo[2,1-f][1,2,4]triazine, quinazolinyl,
quinolyl, thiazolyl, thienyl, and tetrazolyl.

20

In another embodiment, Z is a bond and R^2 is selected
from a 5-10 membered heteroaryl system containing 1-
4 heteroatoms selected from N, O, and S, substituted
with 0-3 R^7 wherein the heteroaryl is selected from
25 indolyl, naphthalenyl, phthalazinyl, cinnolyl,
quinolyl, isoquinolyl, indazolyl, and
quinazolinyl, benzimidazolyl, benzofuranyl,
benzothiofuranyl, benzoxazolyl, benzthiazolyl,
benzisoxazolyl, and benzisothiazolyl.

30

In another embodiment, R^6 , at each occurrence, is
selected from C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl,
(CH_2)_r C_{3-6} cycloalkyl, Cl, Br, I, F, NO_2 , CN,

- $(\text{CH}_2)_r\text{NR}^{6a}\text{R}^{6a}$, $(\text{CH}_2)_r\text{OH}$, $(\text{CH}_2)_r\text{O}(\text{CH}_2)_r\text{R}^{6d}$, $(\text{CH}_2)_r\text{SH}$,
 $(\text{CH}_2)_r\text{C}(\text{O})\text{H}$, $(\text{CH}_2)_r\text{S}(\text{CH}_2)_r\text{R}^{6d}$, $(\text{CH}_2)_r\text{C}(\text{O})\text{OH}$,
 $(\text{CH}_2)_r\text{C}(\text{O})(\text{CH}_2)_r\text{R}^{6b}$, $(\text{CH}_2)_r\text{C}(\text{O})\text{NR}^{6a}\text{R}^{6a}$,
 $(\text{CH}_2)_r\text{NR}^{6f}\text{C}(\text{O})(\text{CH}_2)_r\text{R}^{6b}$, $(\text{CH}_2)_r\text{C}(\text{O})\text{O}(\text{CH}_2)_r\text{R}^{6d}$,
5 $(\text{CH}_2)_r\text{OC}(\text{O})(\text{CH}_2)_r\text{R}^{6b}$, $(\text{CH}_2)_r\text{S}(\text{O})_p(\text{CH}_2)_r\text{R}^{6b}$,
 $(\text{CH}_2)_r\text{S}(\text{O})_2\text{NR}^{6a}\text{R}^{6a}$, $(\text{CH}_2)_r\text{NR}^{6f}\text{S}(\text{O})_2(\text{CH}_2)_r\text{R}^{6b}$,
 $(\text{CH}_2)_r\text{NR}^{6f}\text{S}(\text{O})_2\text{NR}^{6a}\text{R}^{6a}$, C_{1-6} haloalkyl, and
 $(\text{CH}_2)_r$ phenyl substituted with 0-3 R^{6e} ;
- 10 R^{6a} , at each occurrence, is independently selected from H,
methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-
butyl, pentyl, hexyl, cyclopropyl and phenyl;
- 15 R^{6b} , at each occurrence, is selected from methyl, ethyl,
propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl,
hexyl, cyclopropyl, and phenyl;
- 20 R^{6d} , at each occurrence, is selected from methyl, CF_3 ,
ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl,
pentyl, hexyl, cyclopropyl, and phenyl;
- 25 R^{6e} , at each occurrence, is selected from C_{1-6} alkyl, C_{2-8}
alkenyl, C_{2-8} alkynyl, $(\text{CH}_2)_r\text{C}_{3-6}$ cycloalkyl, Cl, F,
Br, I, CN, NO_2 , $(\text{CF}_2)_r\text{CF}_3$, $(\text{CH}_2)_r\text{OC}_{1-5}$ alkyl, OH, SH,
 $(\text{CH}_2)_r\text{SC}_{1-5}$ alkyl, $(\text{CH}_2)_r\text{NR}^{6f}\text{R}^{6f}$, and $(\text{CH}_2)_r$ phenyl; and
- 30 R^{6f} , at each occurrence, is selected from H, methyl,
ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl,
pentyl, hexyl, cyclopropyl, and phenyl.
- In another embodiment, R^6 is selected from methyl, ethyl,
propyl, i-propyl, butyl, F, Cl, Br, I, NO_2 , CN,
 $\text{O}(\text{CH}_2)_r\text{R}^{6d}$, $\text{C}(\text{O})\text{H}$, SR^{6d} , $\text{NR}^{6a}\text{R}^{6a}$, $\text{OC}(\text{O})\text{R}^{6b}$, $\text{S}(\text{O})_p\text{R}^{6b}$,
 $(\text{CHR}')_r\text{S}(\text{O})_2\text{NR}^{6a}\text{R}^{6a}$, CF_3 ;

R^{6a} is H, methyl, or ethyl;

R^{6b} is H or methyl; and

5

R^{6d} is methyl, phenyl, CF₃, and (CH₂)-phenyl.

In another embodiment, R⁷ is selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, s-butyl, t-butyl, pentyl, hexyl, (CH₂)_rC₃₋₆ cycloalkyl, Cl, Br, I, F, NO₂, CN, (CH₂)_rNR^{7a}R^{7a}, (CH₂)_rOH, (CH₂)_rO(CH)_rR^{7d}, (CH₂)_rSH, (CH₂)_rC(O)H, (CH₂)_rS(CH₂)_rR^{7d}, (CH₂)_rC(O)OH, (CH₂)_rC(O)(CH₂)_rR^{7b}, (CH₂)_rC(O)NR^{7a}R^{7a}, (CH₂)_rNR^{7f}C(O)(CH₂)_rR^{7b}, (CH₂)_rC(O)O(CH₂)_rR^{7d}, (CH₂)_rOC(O)(CH₂)_rR^{7b}, (CH₂)_rNR^{7a}C(O)NR^{7a}R^{7a}, (CH₂)_rNR^{7a}C(O)O(CH₂)_rR^{7d}, (CH₂)_rS(O)_p(CH₂)_rR^{7b}, (CH₂)_rS(O)₂NR^{7a}R^{7a}, (CH₂)_rNR^{7f}S(O)₂(CH₂)_rR^{7b}, C₁₋₆ haloalkyl, and (CH₂)_rphenyl substituted with 0-3 R^{7e};

20 R^{7a}, at each occurrence, is selected from H, methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, hexyl, and cyclopropyl;

25 R^{7b}, at each occurrence, is selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, hexyl, and cyclopropyl;

30 R^{7d}, at each occurrence, is selected from methyl, CF₃, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, hexyl, and cyclopropyl;

R^{7e}, at each occurrence, is selected from C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, (CH₂)_rC₃₋₆ cycloalkyl, Cl, F,

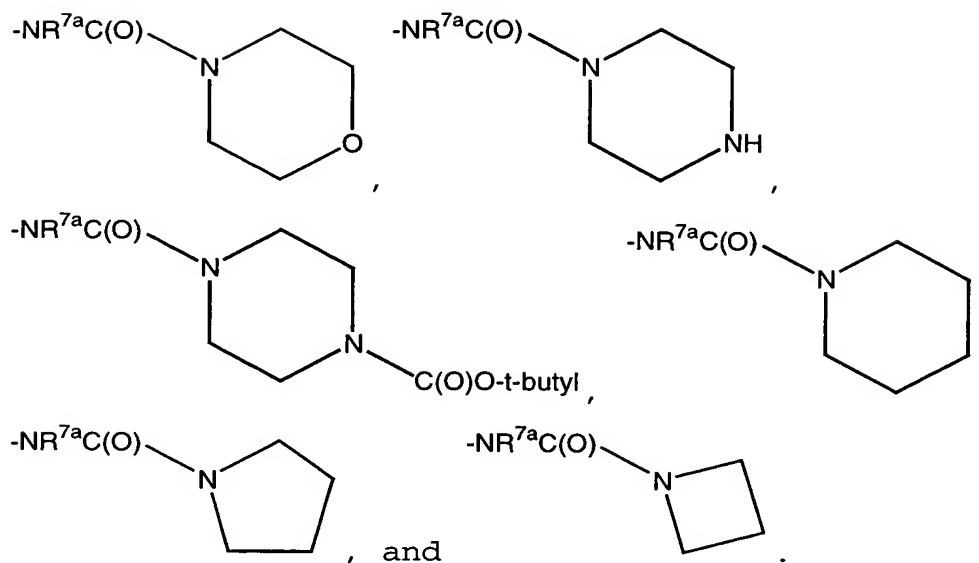
Br, I, CN, NO₂, (CF₂)_rCF₃, (CH₂)_rOC₁₋₅ alkyl, OH, SH,
(CH₂)_rSC₁₋₅ alkyl, (CH₂)_rNR^{7f}R^{7f}, and (CH₂)_rphenyl; and

5 R^{7f}, at each occurrence, is selected from H, methyl,
ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl,
pentyl, hexyl, cyclopropyl, and phenyl.

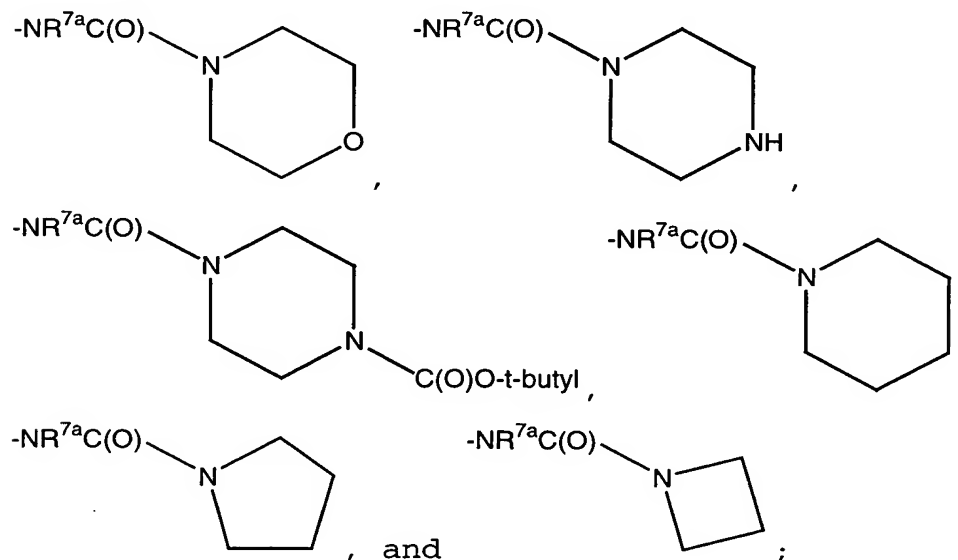
In another embodiment, R⁷ is selected from methyl, ethyl,
propyl, i-propyl, butyl, i-butyl, s-butyl, pentyl,
10 hexyl, Cl, Br, I, F, NO₂, NR^{7a}R^{7a}, NHC(O)NHR^{7a},
NR^{7ac}(O)R^{7b}, NR^{7ac}(O)OR^{7d}, CF₃, OCF₃, C(O)R^{7b},
NR^{7f}C(O)NHR^{7a}, and NHS(O)₂R^{7b}.

In another embodiment, R⁷ is selected from methyl, ethyl,
15 propyl, i-propyl, butyl, i-butyl, s-butyl, t-butyl,
pentyl, hexyl, (CR'R')_rC₃₋₆ cycloalkyl, Cl, Br, I, F,
NO₂, CN, (CR'R')_rNR^{7a}R^{7a}, (CR'R')_rOH,
(CR'R')_rO(CH)_rR^{7d}, (CR'R')_rSH, (CR'R')_rC(O)H,
(CR'R')_rS(CR'R')_rR^{7d}, (CR'R')_rC(O)OH,
20 (CR'R')_rC(O)(CR'R')_rR^{7b}, (CR'R')_rC(O)NR^{7a}R^{7a},
(CR'R')_rNR^{7f}C(O)(CR'R')_rR^{7b}, (CR'R')_rC(O)O(CR'R')_rR^{7d},
(CR'R')_rOC(O)(CR'R')_rR^{7b}, (CR'R')_rNR^{7ac}(O)NR^{7a}R^{7a},
(CR'R')_rNR^{7ac}(O)O(CR'R')_rR^{7d},
(CR'R')_rS(O)_p(CR'R')_rR^{7b}, (CR'R')_rS(O)₂NR^{7a}R^{7a},
25 (CR'R')_rNR^{7f}S(O)₂(CR'R')_rR^{7b}, C₁₋₆ haloalkyl,
adamantyl, and (CR'R')_rphenyl substituted with 0-3
R^{7e}.

In another embodiment, R⁷ is selected from methyl, ethyl,
30 propyl, i-propyl, butyl, i-butyl, s-butyl, pentyl,
hexyl, Cl, Br, I, F, CN, NO₂, NR^{7a}R^{7a}, NHC(O)NHR^{7a},
NR^{7ac}(O)R^{7b}, NR^{7ac}(O)OR^{7d}, CF₃, CF₂CF₃, CHF₂, CH₂F,
OCF₃, C(O)R^{7b}, C(O)OR^{7d}, NR^{7f}C(O)NR^{7a}R^{7a}, NHS(O)₂R^{7b},
adamantyl,



- 5 In another embodiment, R^7 is selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, s-butyl, t-butyl, pentyl, hexyl, phenyl, adamantyl, benzyl, Cl, Br, I, F, CN, NO_2 , $NR^{7a}R^{7a}$, OR^{7d} , $NHC(O)NHR^{7a}$, $NR^{7a}C(O)R^{7b}$, $NR^{7a}C(O)OR^{7d}$, CF_3 , CF_2CF_3 , CHF_2 , CH_2F , OCF_3 , OCF_2CF_3 , $OCHF_2$, and OCH_2F , $C(O)OR^{7d}$, $C(O)R^{7b}$, $NR^{7f}C(O)NR^{7a}R^{7a}$, $NHS(O)_2R^{7b}$,
- 10



15

R^{7a} is selected from H, methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, neo-pentyl,

cyclopropyl, cyclobutyl, cyclopentyl, and
cyclohexyl;

R^{7b} is selected from cyclohexyl and CF₃; and

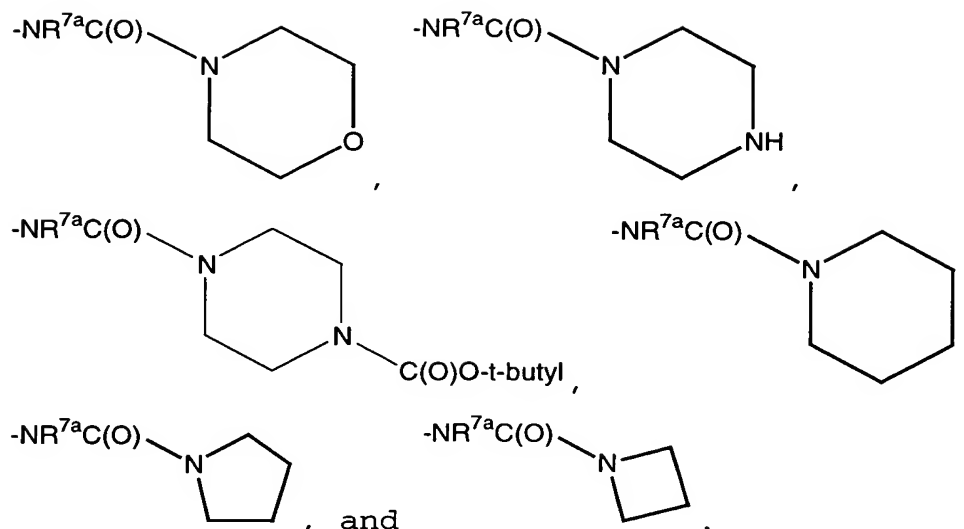
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R^{7d} is selected from methyl, ethyl, propyl, i-propyl,
butyl, i-butyl, and t-butyl.

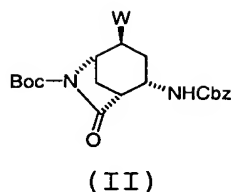
In another embodiment, R⁷ is selected from methyl, ethyl,
10 propyl, i-propyl, butyl, i-butyl, s-butyl, t-butyl,
pentyl, hexyl, phenyl, adamantyl, benzyl, Cl, Br, I,
F, CN, NO₂, NR^{7a}R^{7a}, OR^{7d}, NHC(O)NHR^{7a}, NR^{7ac}(O)R^{7b},
NR^{7ac}(O)OR^{7d}, CF₃, CF₂CF₃, CHF₂, CH₂F, OCF₃, OCF₂CF₃,
OCHF₂, and OCH₂F, C(O)OR^{7d}, C(O)R^{7b}, and
15 NR^{7f}C(O)NR^{7a}R^{7a};

R^{7a} is selected from H, methyl, ethyl, propyl, i-propyl,
butyl, i-butyl, t-butyl, pentyl, neo-pentyl,
20 cyclopropyl, cyclobutyl, cyclopentyl, and
cyclohexyl.

In another embodiment, R⁷ is selected from methyl, ethyl,
propyl, i-propyl, butyl, i-butyl, s-butyl, pentyl,
hexyl, Cl, Br, I, F, NO₂, NR^{7a}R^{7a}, NHC(O)NHR^{7a},
25 NR^{7ac}(O)R^{7b}, NR^{7ac}(O)OR^{7d}, CF₃, OCF₃, C(O)OR^{7d},
C(O)R^{7b}, NR^{7f}C(O)NR^{7a}R^{7a}, NHS(O)₂R^{7b},

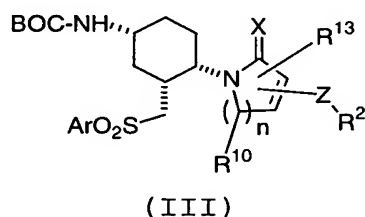


- 5 In another embodiment, R^{7a} is selected from H, methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, neo-pentyl, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl;
- 10 R^{7b} is selected from cyclohexyl and CF_3 ; and
- R^{7d} is selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, and t-butyl.
- 15 In another embodiment, R^8 is H.
- In another embodiment, R^{11} and R^{12} are H.
- 20 In another embodiment, if ring B is not substituted with at least one R^5 which is to $-NR^{5a}R^{5a}$, than Z must be $-NR^8C(O)-$ or $-NR^8C(O)NH-$.
- 25 In another embodiment, the present invention is directed to compounds of formula (II) which are useful as intermediates is the preparation of compounds of formula (I), wherein



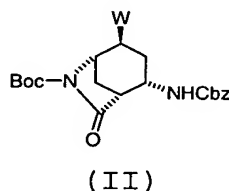
W is H or I.

- 5 In another embodiment, the present invention is directed to compounds of formula (III) which are useful as intermediates in the preparation of compounds of formula (I), wherein

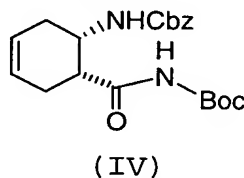


X, Z, R², R¹³, and n are as described above.

- 15 In another embodiment, the present invention is directed to process of preparing compounds of formula (II), wherein

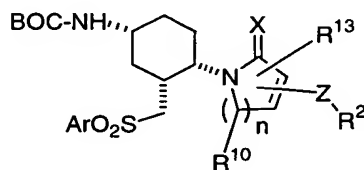


- 20 W is H or I;
comprising converting a compound of formula (IV)



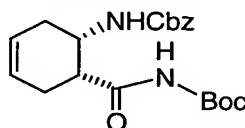
- 25 into a compound of formula (II) by use of an electrophile and base.

In another embodiment, the present invention is directed to process of preparing a compound of formula (III),



(III)

X, Z, R², R¹³, and n are as described above, comprising converting a compound of formula (IV)

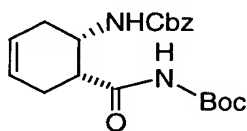


(IV)

into a compound of formula (II) by use of an electrophile and base.

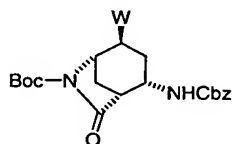
In another embodiment, the present invention is directed to process of preparing compounds of formula (I), comprising

converting a compound of formula (IV)



(IV)

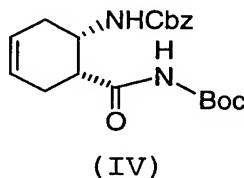
into a compound of formula (II) by use of an electrophile and base



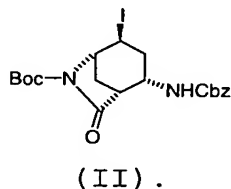
(II) .

In another embodiment, the present invention is directed to process of preparing compounds of formula (I), comprising

- 5 converting a compound of formula (IV)

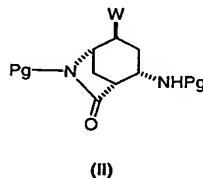


- 10 into a compound of formula (II) by use of an electrophile and base, wherein the base is Butyl lithium and the electrophile is iodine



15

In another embodiment, the present invention is directed compound of Formula (II)



- 20 or salt or stereoisomer thereof, wherein

W is selected from H, I, and Br;

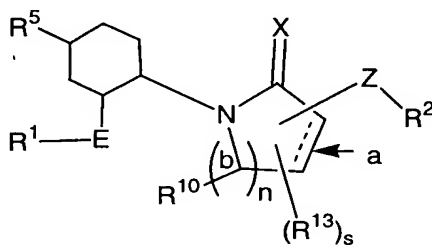
- 25 Pg, at each occurrence, is independently selected from an amine protecting group.

In another embodiment, the present invention is directed to a compound of formula (II), wherein

W is selected from H, I, and Br; and

Pg, at each occurrence, is independently selected from
 5 benzyloxycarbonyl (Cbz) and tert-butyloxycarbonyl
 (Boc).

In another embodiment, the present invention is
 directed to a process of preparing a compound of formula
 10 (Ia),



(Ia)

or salt or stereoisomer thereof: wherein

15 E is selected from $-S(O)_pCHRe-$, $-CHReNRe-$, $-C(O)-NRe-$,
 $-NReC(O)NRe-$, $-SO_2-NRe-$, and $-NReSO_2NRe-$;

Re is independently selected from H and C_{1-3} alkyl;

20 X is selected from O or S;

Z is selected from a bond, $-NR^8C(O)-$, $-NR^8C(S)-$,
 $-NR^8C(O)NH-$, $-NR^8C(S)NH-$, $-NR^8SO_2-$, $-NR^8SO_2NH-$,
 $-C(O)NR^8-$, $-OC(O)NR^8-$, $-NR^8C(O)O-$, $-(CR^{15}R^{15})_1-$,
 25 $-CR^{14}=CR^{14}-$, $-CR^{15}R^{15}C(O)-$, $-C(O)CR^{15}R^{15}-$,
 $CR^{15}R^{15}C(=N-OR^{16})-$, $-O-CR^{14}R^{14}-$, $-CR^{14}R^{14}-O-$, $-O-$,
 $-NR^9-$, $-NR^9-CR^{14}R^{14}-$, $-CR^{14}R^{14}-NR^9-$, $-S(O)_p-$, $-S(O)_p-$
 $CR^{14}R^{14}-$, $-CR^{14}R^{14}-S(O)_p-$, and $-S(O)_p-NR^9-$;

wherein neither Z nor R^{13} are connected to a carbon atom labeled (b);

bond (a) is a single or double bond;

5

alternatively, when n is equal to 2, two atoms labeled (b) may join through a double bond;

10 R^1 is selected from a C_{6-10} aryl group substituted with 0-5 R^6 and a 5-10 membered heteroaryl system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^6 ;

15 R^2 is selected from a C_{6-10} aryl group substituted with 0-5 R^7 and a 5-10 membered heteroaryl system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^7 ;

20 R^5 , at each occurrence, is independently selected from H, $(CRR)_rOH$, $(CRR)_rSH$, $(CRR)_rOR^{5d}$, $(CRR)_rSR^{5d}$, $(CRR)_rNR^{5a}R^{5a}$, $(CRR)_rN(\rightarrow O)R^{5a}R^{5a}$, $(CRR)_rNR^{5a}C(O)R^{5b}$, $(CRR)_rOC(O)NR^{5a}R^{5a}$, $(CRR)_rNR^{5a}C(O)OR^{5d}$, $(CRR)_rNR^{5a}C(O)NR^{5a}R^{5a}$, $(CRR)_rNR^{5a}C(O)H$, $(CRR)_rOC(O)R^{5b}$, $(CRR)_rS(O)_pR^{5b}$, $(CRR)_rS(O)_2NR^{5a}R^{5a}$,
25 $(CRR)_rNR^{5a}S(O)_2R^{5b}$, $(CRR)_rNR^{5a}S(O)_2NR^{5a}R^{5a}$, and a $(CRR)_r$ -5-10 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-2 R^{5c} ;

30 R^{5a} , at each occurrence, is independently selected from H, methyl substituted with 0-1 R^{5g} , C_{2-6} alkyl substituted with 0-2 R^{5e} , C_{3-8} alkenyl substituted with 0-2 R^{5e} , C_{3-8} alkynyl substituted with 0-2 R^{5e} , a $(CH_2)_r$ - C_{3-10} carbocyclic residue substituted with

0-5 R^{5e}, and a (CH₂)_r-5-10 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{5e};

5 R^{5b}, at each occurrence, is selected from C₁₋₆ alkyl substituted with 0-3 R^{5e}, C₃₋₈ alkenyl substituted with 0-2 R^{5e}, C₃₋₈ alkynyl substituted with 0-2 R^{5e}, a (CH₂)_r-C₃₋₆ carbocyclic residue substituted with 0-2 R^{5e}, and a (CH₂)_r-5-6 membered heterocyclic
10 system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{5e};

R^{5c}, at each occurrence, is selected from C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, (CH₂)_r-C₃₋₆ cycloalkyl, Cl, Br,
15 I, F, (CF₂)_rCF₃, NO₂, CN, (CH₂)_rNR^{5f}R^{5f}, (CH₂)_rOH, (CH₂)_rOC₁₋₄ alkyl, (CH₂)_rSC₁₋₄ alkyl, (CH₂)_rC(O)OH, (CH₂)_rC(O)R^{5b}, (CH₂)_rC(O)NR^{5f}R^{5f}, (CH₂)_rOC(O)NR^{5f}R^{5f}, (CH₂)_rNR^{5f}C(O)R^{5b}, (CH₂)_rC(O)OC₁₋₄ alkyl, (CH₂)_rNR^{5f}C(O)OC₁₋₄ alkyl, (CH₂)_rOC(O)R^{5b},
20 (CH₂)_rC(=NR^{5f})NR^{5f}R^{5f}, (CH₂)_rS(O)_pR^{5b}, (CH₂)_rNHC(=NR^{5f})NR^{5f}R^{5f}, (CH₂)_rS(O)₂NR^{5f}R^{5f}, (CH₂)_rNR^{5f}S(O)₂R^{5b}, and (CH₂)_rphenyl substituted with 0-3 R^{5e};

25 R^{5d}, at each occurrence, is selected from methyl, CF₃, C₂₋₆ alkyl substituted with 0-2 R^{5e}, C₃₋₈ alkenyl substituted with 0-2 R^{5e}, C₃₋₈ alkynyl substituted with 0-2 R^{5e}, and a C₃₋₁₀ carbocyclic residue substituted with 0-3 R^{5e};

30 R^{5e}, at each occurrence, is selected from C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₆ cycloalkyl, Cl, F, Br, I,

CN, NO₂, (CF₂)_rCF₃, (CH₂)_rOC₁₋₅ alkyl, OH, SH,
 (CH₂)_rSC₁₋₅ alkyl, (CH₂)_rNR^{5f}R^{5f}, and (CH₂)_rphenyl;

5 R^{5f}, at each occurrence, is selected from H, C₁₋₆ alkyl,
 and C₃₋₆ cycloalkyl;

R^{5g} is independently selected from -C(O)R^{5b}, -C(O)OR^{5d},
 -C(O)NR^{5f}R^{5f}, -CN, and (CH₂)_rphenyl;

10 R, at each occurrence, is selected from H, C₁₋₆ alkyl
 substituted with R^{5e}, C₂₋₈ alkenyl, C₂₋₈ alkynyl,
 (CH₂)_rC₃₋₆ cycloalkyl, and (CH₂)_rphenyl substituted
 with R^{5e};

15 R⁶, at each occurrence, is selected from C₁₋₈ alkyl, C₂₋₈
 alkenyl, C₂₋₈ alkynyl, (CH₂)_rC₃₋₆ cycloalkyl, Cl, Br,
 I, F, NO₂, CN, (CR'R')_rNR^{6a}R^{6a}, (CR'R')_rOH,
 (CR'R')_rO(CR'R')_rR^{6d}, (CR'R')_rSH, (CR'R')_rC(O)H,
 (CR'R')_rS(CR'R')_rR^{6d}, (CR'R')_rSC(O)(CR'R')_rR^{6b},
 20 (CR'R')_rC(O)OH, (CR'R')_rC(O)(CR'R')_rR^{6b},
 (CR'R')_rNR^{6a}R^{6a}, (CR'R')_rC(O)NR^{6a}R^{6a},
 (CR'R')_rNR^{6f}C(O)(CR'R')_rR^{6b}, (CR'R')_rC(O)O(CR'R')_rR^{6d},
 (CR'R')_rOC(O)(CR'R')_rR^{6b},
 (CR'R')_rOC(O)NR^{6a}(CR'R')_rR^{6d},
 25 (CR'R')_rNR^{6a}C(O)NR^{6a}(CR'R')_rR^{6d},
 (CR'R')_rNR^{6a}C(S)NR^{6a}(CR'R')_rR^{6d},
 (CR'R')_rNR^{6f}C(O)O(CR'R')_rR^{6b}, (CR'R')_rC(=NR^{6f})NR^{6a}R^{6a},
 (CR'R')_rNHC(=NR^{6f})NR^{6f}R^{6f}, (CR'R')_rS(O)_p(CR'R')_rR^{6b},
 (CR'R')_rS(O)₂NR^{6a}R^{6a}, (CR'R')_rNR^{6f}S(O)₂NR^{6a}R^{6a},
 30 (CR'R')_rNR^{6f}S(O)₂(CR'R')_rR^{6b}, C₁₋₆ haloalkyl, C₂₋₈
 alkenyl substituted with 0-3 R', C₂₋₈ alkynyl
 substituted with 0-3 R', (CR'R')_rphenyl substituted
 with 0-3 R^{6e}, and a (CH₂)_{r-5-6} membered heterocyclic

system containing 1-2 heteroatoms selected from N, O, and S, substituted with 0-2 R^{6e};

alternatively, two R⁶ on adjacent atoms on R¹ may join to
5 form a cyclic acetal;

R^{6a}, at each occurrence, is selected from H, methyl substituted with 0-1 R^{6g}, C₂₋₆ alkyl substituted with 0-2 R^{6e}, C₃₋₈ alkenyl substituted with 0-2 R^{6e}, C₃₋₈
10 alkynyl substituted with 0-2 R^{6e}, a (CH₂)_r-C₃₋₁₀ carbocyclic residue substituted with 0-5 R^{6e}, and a (CH₂)_r-5-10 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-2 R^{6e};

15 R^{6b}, at each occurrence, is selected from H, C₁₋₆ alkyl substituted with 0-2 R^{6e}, C₃₋₈ alkenyl substituted with 0-2 R^{6e}, C₃₋₈ alkynyl substituted with 0-2 R^{6e}, a (CH₂)_r-C₃₋₆ carbocyclic residue substituted with 0-3
20 R^{6e}, and a (CH₂)_r-5-6 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-2 R^{6e};

R^{6d}, at each occurrence, is selected from C₃₋₈ alkenyl substituted with 0-2 R^{6e}, C₃₋₈ alkynyl substituted with 0-2 R^{6e}, methyl, CF₃, C₂₋₆ alkyl substituted with 0-3 R^{6e}, C₂₋₄ haloalkyl, a (CH₂)_r-C₃₋₁₀
25 carbocyclic residue substituted with 0-3 R^{6e}, and a (CH₂)_r-5-6 membered heterocyclic system containing
30 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{6e};

R^{6e}, at each occurrence, is selected from C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, (CH₂)_r-C₃₋₆ cycloalkyl, Cl, F,

Br, I, CN, NO₂, (CF₂)_rCF₃, (CH₂)_rOC₁₋₅ alkyl, OH, SH,
(CH₂)_rSC₁₋₅ alkyl, (CH₂)_rNR^{6f}R^{6f}, and (CH₂)_rphenyl;

5 R^{6f}, at each occurrence, is selected from H, C₁₋₅ alkyl,
and C₃₋₆ cycloalkyl, and phenyl;

R^{6g} is independently selected from -C(O)R^{6b}, -C(O)OR^{6d},
-C(O)NR^{6f}R^{6f}, and (CH₂)_rphenyl;

10 R⁷, at each occurrence, is selected from C₁₋₈ alkyl, C₂₋₈
alkenyl, C₂₋₈ alkynyl, (CH₂)_rC₃₋₆ cycloalkyl, Cl, Br,
I, F, NO₂, CN, (CR'R')_rNR^{7a}R^{7a}, (CR'R')_rOH,
(CR'R')_rO(CR'R')_rR^{7d}, (CR'R')_rSH, (CR'R')_rC(O)H,
(CR'R')_rS(CR'R')_rR^{7d}, (CR'R')_rC(O)OH,
15 (CR'R')_rC(O)(CR'R')_rR^{7b}, (CR'R')_rC(O)NR^{7a}R^{7a},
(CR'R')_rNR^{7f}C(O)(CR'R')_rR^{7b}, (CR'R')_rC(O)O(CR'R')_rR^{7d},
(CR'R')_rOC(O)(CR'R')_rR^{7b},
(CR'R')_rOC(O)NR^{7a}(CR'R')_rR^{7a},
(CR'R')_rNR^{7a}C(O)NR^{7a}(CR'R')_rR^{7a},
20 (CR'R')_rNR^{7f}C(O)O(CR'R')_rR^{7d}, (CR'R')_rC(=NR^{7f})NR^{7a}R^{7a},
(CR'R')_rNHC(=NR^{7f})NR^{7f}R^{7f}, (CR'R')_rS(O)_p(CR'R')_rR^{7b},
(CR'R')_rS(O)₂NR^{7a}R^{7a}, (CR'R')_rNR^{7a}S(O)₂NR^{7a}R^{7a},
(CR'R')_rNR^{7f}S(O)₂(CR'R')_rR^{7b}, C₁₋₆ haloalkyl, C₂₋₈
alkenyl substituted with 0-3 R', C₂₋₈ alkynyl
25 substituted with 0-3 R', (CR'R')_r C₃₋₁₀ carbocyclic
residue and (CR'R')_rphenyl substituted with 0-3 R^{7e};

alternatively, two R⁷ on adjacent atoms on R² may join to
form a cyclic acetal;

30

R^{7a}, at each occurrence, is independently selected from H,
methyl substituted with 0-1 R^{7g}, C₂₋₆ alkyl
substituted with 0-2 R^{7e}, C₃₋₈ alkenyl substituted

with 0-2 R^{7e}, C₃₋₈ alkynyl substituted with 0-2 R^{7e},
 a (CH₂)_r-C₃₋₁₀ carbocyclic residue substituted with
 0-5 R^{7e}, and a (CH₂)_r-5-10 membered heterocyclic
 system containing 1-4 heteroatoms selected from N,
 5 O, and S, substituted with 0-2 R^{7e};

R^{7b}, at each occurrence, is selected from C₁₋₆ alkyl
 substituted with 0-2 R^{7e}, C₃₋₈ alkenyl substituted
 with 0-2 R^{7e}, C₃₋₈ alkynyl substituted with 0-2 R^{7e},
 10 a (CH₂)_r-C₃₋₆ carbocyclic residue substituted with 0-3
 R^{7e}, and a (CH₂)_r-5-6 membered heterocyclic system
 containing 1-4 heteroatoms selected from N, O, and
 S, substituted with 0-2 R^{7e};

15 R^{7d}, at each occurrence, is selected from C₃₋₈ alkenyl
 substituted with 0-2 R^{7e}, C₃₋₈ alkynyl substituted
 with 0-2 R^{7e}, methyl, CF₃, C₂₋₄ haloalkyl, C₂₋₆ alkyl
 substituted with 0-3 R^{7e}, a (CH₂)_r-C₃₋₁₀ carbocyclic
 residue substituted with 0-3 R^{7e}, and a (CH₂)_r-5-6
 20 membered heterocyclic system containing 1-4
 heteroatoms selected from N, O, and S, substituted
 with 0-3 R^{7e};

R^{7e}, at each occurrence, is selected from C₁₋₆ alkyl, C₂₋₈
 25 alkenyl, C₂₋₈ alkynyl, (CH₂)_r-C₃₋₆ cycloalkyl, Cl, F,
 Br, I, CN, NO₂, (CF₂)_rCF₃, (CH₂)_rOC₁₋₅ alkyl, OH, SH,
 C(O)OC₁₋₅ alkyl, (CH₂)_rSC₁₋₅ alkyl, (CH₂)_rNR^{7f}R^{7f}, and
 (CH₂)_rphenyl;

30 R^{7f}, at each occurrence, is selected from H, C₁₋₅ alkyl,
 and C₃₋₆ cycloalkyl, and phenyl;

R^{7g} is independently selected from -C(O)R^{7b}, -C(O)OR^{7d},
 -C(O)NR^{7f}R^{7f}, and (CH₂)_rphenyl;

R', at each occurrence, is selected from H, C₁₋₆ alkyl
substituted with R^{6e}, C₂₋₈ alkenyl, C₂₋₈ alkynyl,
(CH₂)_rC₃₋₆ cycloalkyl, and (CH₂)_rphenyl substituted
5 with R^{6e};

R⁸ is selected from H, C₁₋₄ alkyl, and C₃₋₄ cycloalkyl;

R⁹ is selected from H, C₁₋₄ alkyl, C₃₋₄ cycloalkyl,
10 -C(O)H, and -C(O)-C₁₋₄alkyl;

R¹⁰ is independently selected from H, and C₁₋₄alkyl
substituted with 0-1 R^{10b}, alternatively, two R¹⁰
form =O;
15

R^{10b}, at each occurrence, is independently selected from
-OH, -SH, -NR^{10c}R^{10c}, -C(O)NR^{10c}R^{10c}, and -NHC(O)R^{10c};

R^{10c} is selected from H, C₁₋₄ alkyl and C₃₋₆ cycloalkyl;
20

R¹⁴, at each occurrence, is independently selected from H
and C₁₋₄alkyl;

alternatively, two R¹⁴s, along with the carbon atom to
25 which they are attached, join to form a C₃₋₆
carbocyclic ring;

R¹⁵, at each occurrence, is independently selected from H,
C₁₋₄alkyl, OH, NH₂, -O-C₁₋₄ alkyl, NR^{15a}R^{15a},
30 C(O)NR^{15a}R^{15a}, NR^{15a}C(O)R^{15b}, NR^{15a}C(O)OR^{15d},
OC(O)NR^{15a}R^{15a}, and (CHR)_rC(O)OR^{15d};

alternatively, two R¹⁵s, along with the carbon atom or atoms to which they are attached, join to form a C₃₋₆ carbocyclic ring;

5 R^{15a}, at each occurrence, is independently selected from H, and C₁₋₄ alkyl;

R^{15b}, at each occurrence, is independently selected from C₁₋₄ alkyl, C₃₋₆ alkenyl, and C₃₋₆ alkynyl;

10

R^{15d}, at each occurrence, is independently selected from C₁₋₄ alkyl, C₃₋₆ alkenyl, and C₃₋₆ alkynyl;

R¹⁶ is selected from C₁₋₄ alkyl;

15

l is selected from 1, 2 and 3;

n is selected from 0, 1, 2, and 3;

20 p, at each occurrence, is independently selected from 0, 1, and 2;

q, at each occurrence, is independently selected from 1, 2, 3, and 4;

25

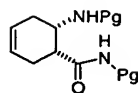
r, at each occurrence, is independently selected from 0, 1, 2, 3, and 4;

s is selected from 0 and 1; and

30

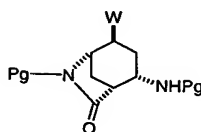
t, at each occurrence, is independently selected from 2, 3, and 4;

the steps comprising reacting a compound of Formula IV,



(IV)

5 with an electrophile and base to give a compound of
Formula II;



(II)

wherein

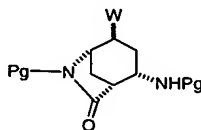
10 W is selected from H, I, and Br;

Pg, at each occurrence, is independently selected from an
amine protecting group;

15 reacting a compound of Formula II to give the compound of
Formula (Ia).

In another embodiment, the present invention is
directed to a process of preparing a compound of Formula

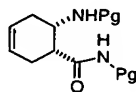
20 (II), wherein



(II)

or salt or stereoisomer thereof,

25 comprising reacting a compound of Formula (IV)



(IV)

with an electrophile and a base,

wherein

5 W is selected from I and Br;

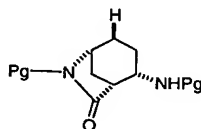
Pg, at each occurrence, is independently selected from an amine protecting group.

10 In another embodiment, the present invention is directed to a process of preparing a compound of Formula (II), wherein

the electrophile is selected from iodine, bromine, N-
15 bromo-succimide, and N-iodosuccinimide; and

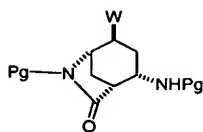
the base is selected from n-butyl lithium, lithium
diisopropylamide (LDA), sodium hydride, lithium
bis(trimethylsilyl)amide, potassium
20 bis(trimethylsilyl)amide, sodium
bis(trimethylsilyl)-amide, and Li-Al(O-tButyl)₄.

In another embodiment, the present invention is
directed to a process of preparing a compound of Formula
25 (IIa), wherein



(IIa)

comprising reduction of a compound of Formula (II) with a reducing agent;



(II)

wherein W is selected from I and Br , and

Pg, at each occurrence, is independently selected from an
 5 amine protecting group.

In another embodiment, the present invention is directed to a process of preparing a compound of Formula (IIa), wherein the reducing agent is selected from tris-
 10 (trimethylsilyl)silane, zinc metal, tributyltin hydride and AIBN.

The invention may be embodied in other specific forms without departing from the spirit or essential
 15 attributes thereof. This invention also encompasses all combinations of alternative aspects of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment to describe
 20 additional embodiments of the present invention. Furthermore, any elements of an embodiment are meant to be combined with any and all other elements from any of the embodiments to describe additional embodiments.

25 DEFINITIONS

The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in
 30 the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric

isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the
5 compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric
10 form is specifically indicated.

The processes of the present invention are contemplated to be practiced on at least a multigram scale, kilogram scale, multikilogram scale, or industrial scale. Multigram scale, as used herein, is preferably
15 the scale wherein at least one starting material is present in 10 grams or more, more preferably at least 50 grams or more, even more preferably at least 100 grams or more. Multikilogram scale, as used herein, is intended to mean the scale wherein more than one kilogram of at
20 least one starting material is used. Industrial scale as used herein is intended to mean a scale which is other than a laboratory scale and which is sufficient to supply product sufficient for either clinical tests or distribution to consumers.

25 Suitable ether solvents include, but are not intended to be limited to, dimethoxymethane, tetrahydrofuran, 1,3-dioxane, 1,4-dioxane, furan, diethyl ether, ethylene glycol dimethyl ether, ethylene glycol diethyl ether, diethylene glycol dimethyl ether, diethylene glycol
30 diethyl ether, triethylene glycol dimethyl ether, or t-butyl methyl ether. Suitable hydrocarbon solvents include, but are not intended to be limited to, benzene, cyclohexane, pentane, hexane, toluene, cycloheptane,

methylcyclohexane, heptane, ethylbenzene, m-, o-, or p-xylene, octane, indane, nonane, or naphthalene.

As used herein, the term "amine protecting group" (or "N-protected") refers to any group known in the art of organic synthesis for the protection of amine groups. As used herein, the term "amine protecting group reagent" refers to any reagent known in the art of organic synthesis for the protection of amine groups which may be reacted with an amine to provide an amine protected with an amine protecting group. The "amine protecting group" should be compatible with other reaction conditions. Such amine protecting groups include those listed in Greene and Wuts, "Protective Groups in Organic Synthesis" John Wiley & Sons, New York (1991) and "The Peptides: Analysis, Synthesis, Biology, Vol. 3, Academic Press, New York (1981), the disclosure of which is hereby incorporated by reference. Examples of amine protecting groups include, but are not limited to, the following: 1) acyl types such as formyl, trifluoroacetyl, and p-toluenesulfonyl; 2) aromatic carbamate types such as benzyloxycarbonyl (Cbz) and substituted benzyloxycarbonyls, 1-(p-biphenyl)-1-methylethoxycarbonyl, and 9-fluorenylmethyloxycarbonyl (Fmoc); 3) aliphatic carbamate types such as tert-butyloxycarbonyl (Boc), ethoxycarbonyl, diisopropylmethoxycarbonyl, and allyloxycarbonyl; and 4) cyclic alkyl carbamate types such as cyclopentyloxycarbonyl and adamantyloxycarbonyl.

Amine protecting groups may include, but are not limited to the following: 2,7-di-t-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyloxycarbonyl; 2-trimethylsilylethyloxycarbonyl; 2-phenylethyloxycarbonyl;

1,1-dimethyl-2,2-dibromoethyloxycarbonyl; 1-methyl-1-(4-biphenyl)ethyloxycarbonyl; benzyloxycarbonyl; p-nitrobenzyloxycarbonyl; 2-(p-toluenesulfonyl)ethyloxycarbonyl; m-chloro-p-acyloxybenzyloxycarbonyl; 5-benzyisoxazolylmethyloxycarbonyl; p-(dihydroxyboryl)benzyloxycarbonyl; m-nitrophenyloxycarbonyl; o-nitrobenzyloxycarbonyl; 3,5-dimethoxybenzyloxycarbonyl; 3,4-dimethoxy-6-nitrobenzyloxycarbonyl; N'-p-toluenesulfonylaminocarbonyl; t-amylloxycarbonyl; p-decyloxybenzyloxycarbonyl; diisopropylmethyloxycarbonyl; 2,2-dimethoxycarbonylvinyloxycarbonyl; di(2-pyridyl)methyloxycarbonyl; or 2-furanylmethyloxycarbonyl.

A suitable selective reducing agent is a reagent or combination of reagents which will selectively reduce the W group in the compound of Formula (II) to a hydrogen without altering the character of the other substitutents. Suitable selective reducing agents include, but are not limited to, tris-(trimethylsilyl)silane, zinc metal, tributyltin hydride and catalytic versions, see Gregory Fu, *Org. Syn.* (2002), 78, 239-248 which is hereby incorporated by reference, and AIBN (2,2'-Azobisisobutyronitrile).

One enantiomer of a compound of Formula I may display superior activity compared with the other. Thus, all of the stereochemistries are considered to be a part of the present invention. When required, separation of the racemic material can be achieved by HPLC using a chiral column or by a resolution using a resolving agent such as camphonic chloride as in Steven D. Young, et al, *Antimicrobial Agents and Chemotherapy*, **1995**, 2602-2605.

The term "substituted," as used herein, means that any one or more hydrogens on the designated atom or ring is replaced with a selection from the indicated group, provided that the designated atom's or ring atom's normal
5 valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

When any variable (e.g., R^{10}) occurs more than one time in any constituent or formula for a compound, its
10 definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^{10} , then said group may optionally be substituted with up to two R^{10} groups and R^{10} at each occurrence is selected
15 independently from the definition of R^{10} . Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a
20 bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be
25 bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein, "C₁₋₈ alkyl" is intended to include both branched and straight-chain saturated aliphatic
30 hydrocarbon groups having the specified number of carbon atoms, examples of which include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, pentyl, and hexyl. C₁₋₈ alkyl, is intended

to include C₁, C₂, C₃, C₄, C₅, C₆, C₇, and C₈ alkyl groups. "Alkenyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in
5 any stable point along the chain, such as ethenyl, propenyl, and the like. "Alkynyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more unsaturated triple carbon-carbon bonds which may occur in any stable point along
10 the chain, such as ethynyl, propynyl, and the like. "C₃₋₆ cycloalkyl" is intended to include saturated ring groups having the specified number of carbon atoms in the ring, including mono-, bi-, or poly-cyclic ring systems, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and
15 cycloheptyl in the case of C₇ cycloalkyl. C₃₋₆ cycloalkyl, is intended to include C₃, C₄, C₅, and C₆ cycloalkyl groups

"Halo" or "halogen" as used herein refers to fluoro, chloro, bromo, and iodo; and "haloalkyl" is intended to
20 include both branched and straight-chain saturated aliphatic hydrocarbon groups, for example CF₃, having the specified number of carbon atoms, substituted with 1 or more halogen (for example -C_vF_w where v = 1 to 3 and w = 1 to (2v+1)).

25 As used herein, the term "5-6-membered cyclic ketal" is intended to mean 2,2-disubstituted 1,3-dioxolane or 2,2-disubstituted 1,3-dioxane and their derivatives.

As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3, 4, 5, 6, or 7-
30 membered monocyclic or bicyclic or 7, 8, 9, 10, 11, 12, or 13-membered bicyclic or tricyclic, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to,

cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,
 cycloheptyl, adamantyl, cyclooctyl,;
 [3.3.0]bicyclooctane, [4.3.0]bicyclononane,
 [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane,
 5 fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or
 tetrahydronaphthyl (tetralin).

As used herein, the term "heterocycle" or
 "heterocyclic system" is intended to mean a stable 5, 6,
 or 7-membered monocyclic or bicyclic or 7, 8, 9, or 10-
 10 membered bicyclic heterocyclic ring which is saturated,
 partially unsaturated or unsaturated (aromatic), and
 which consists of carbon atoms and 1, 2, 3, or 4
 heteroatoms independently selected from the group
 consisting of N, NH, O and S and including any bicyclic
 15 group in which any of the above-defined heterocyclic
 rings is fused to a benzene ring. The nitrogen and
 sulfur heteroatoms may optionally be oxidized. The
 heterocyclic ring may be attached to its pendant group at
 any heteroatom or carbon atom which results in a stable
 20 structure. The heterocyclic rings described herein may
 be substituted on carbon or on a nitrogen atom if the
 resulting compound is stable. If specifically noted, a
 nitrogen in the heterocycle may optionally be
 quaternized. It is preferred that when the total number
 25 of S and O atoms in the heterocycle exceeds 1, then these
 heteroatoms are not adjacent to one another. As used
 herein, the term "aromatic heterocyclic system" or
 "heteroaryl" is intended to mean a stable 5- to 7-
 membered monocyclic or bicyclic or 7- to 10-membered
 30 bicyclic heterocyclic aromatic ring which consists of
 carbon atoms and from 1 to 4 heterotams independently
 selected from the group consisting of N, O and S and is
 aromatic in nature.

Examples of heterocycles include, but are not
 35 limited to, 1H-indazole, 2-pyrrolidonyl, 2H,6H-1,5,2-
 dithiazinyl, 2H-pyrrolyl, 1H-indolyl, 4-piperidonyl, 4aH-

carbazole, 4H-quinoliziny, 6H-1,2,5-thiadiaziny, acridiny, azociny, benzimidazolyl, benzofurany, benzothiofurany, benzothiopheny, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl,

5 benzisoxazolyl, benzisothiazolyl, benzimidazalonyl, carbazolyl, 4aH-carbazolyl, β -carboliny, chromany, chromeny, cinnoliny, decahydroquinoliny, 2H,6H-1,5,2-dithiaziny, dihydrofuro[2,3-b]tetrahydrofuran, furany, furazany, imidazolidiny, imidazoliny, imidazolyl,

10 indazolyl, indoleny, indoliny, indoliziny, indoly, isobenzofurany, isochromany, isoindazolyl, isoindoliny, isoindoly, isoquinoliny (benzimidazolyl), isothiazolyl, isoxazolyl, morpholiny, naphthyridiny, octahydroisoquinoliny, oxadiazolyl, 1,2,3-oxadiazolyl,

15 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidiny, oxazolyl, oxazolidiny, perimidiny, phenanthridiny, phenanthroliny, phenarsaziny, phenaziny, phenothiaziny, phenoxathiiny, phenoxaziny, phthalaziny, piperaziny, piperidiny, pteridiny,

20 piperidony, 4-piperidony, pteridiny, puriny, pyranly, pyraziny, pyrazolidiny, pyrazoliny, pyrazolyl, pyridaziny, pyridooxazole, pyridoimidazole, pyridothiazole, pyridiny, pyridyl, pyrimidiny, pyrrolidiny, pyrroliny, pyrroly, quinazoliny,

25 quinoliny, 4H-quinoliziny, quinoxaliny, quinuclidiny, carboliny, tetrahydrofurany, tetrahydroisoquinoliny, tetrahydroquinoliny, 6H-1,2,5-thiadiaziny, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthreny, thiazolyl, thieny,

30 thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiopheny, triaziny, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, tetrazolyl, and xantheny. In another aspect of the invention, the

heterocycles include, but are not limited to, pyridiny,

35 thiopheny, furany, indazolyl, benzothiazolyl, benzimidazolyl, benzothiapheny, benzofurany, benzoxazolyl, benzisoxazolyl, quinoliny, isoquinoliny,

imidazolyl, indolyl, isoidolyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pyrrazolyl, 1,2,4-triazolyl, 1,2,3-triazolyl, tetrazolyl, thiazolyl, oxazolyl, pyrazinyl, and pyrimidinyl. Also included are fused ring
 5 and spiro compounds containing, for example, the above heterocycles.

Examples of heteroaryls are 1H-indazole, 2H,6H-1,5,2-dithiazinyl, indolyl, 4aH-carbazole, 4H-quinoliziny, 6H-1,2,5-thiadiazinyl, acridinyl, azocinyl,
 10 benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalonyl, carbazolyl, 4aH-carbazolyl, β -carbolinyl, chromanyl, chromenyl,
 15 cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, indazolyl, indolenyl, indolinyl, indoliziny, indolyl, isobenzofuranyl, isochromanyl, isoindazolyl,
 20 isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinylperimidinyl,
 25 phenanthridinyl, phenanthrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, piperidonyl, 4-piperidonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole,
 30 pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinoliziny, quinoxalinyl, quinuclidinyl, carbolinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl,

thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, tetrazolyl, and xanthenyl. In another aspect of the invention, examples of heteroaryls are indolyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalonyl, cinnolinyl, furanyl, imidazolyl, indazolyl, indolyl, isoquinolinyl isothiazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyridinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, thiazolyl, thienyl, and tetrazolyl.

As used herein, the term "cyclic acetal" or the phrase when two variables "join to form a cyclic acetal" is intended to mean the substituent $-O-CH_2-O-$.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the

quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, 5 hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, 10 salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound 15 which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a 20 mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the 25 disclosure of which is hereby incorporated by reference.

Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc...) the compounds of the present invention may be delivered in prodrug form. 30 Thus, the present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions containing the same. "Prodrugs" are intended to include any covalently bonded carriers which release an active parent drug of the

present invention *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs the present invention are prepared by modifying functional groups present in the compound in such a way that the
5 modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of the present invention wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug of the present invention is administered
10 to a mammalian subject, it cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of
15 the present invention.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious
20 therapeutic agent. The present invention is intended to embody stable compounds.

"Therapeutically effective amount" is intended to include an amount of a compound of the present invention alone or an amount of the combination of compounds
25 claimed or an amount of a compound of the present invention in combination with other active ingredients effective to inhibit MCP-1 or effective to treat or prevent inflammatory disorders.

As used herein, "treating" or "treatment" cover the
30 treatment of a disease-state in a mammal, particularly in a human, and include: (a) preventing the disease-state from occurring in a mammal, in particular, when such mammal is predisposed to the disease-state but has not yet been diagnosed as having it; (b) inhibiting the
35 disease-state, i.e., arresting its development; and/or (c) relieving the disease-state, i.e., causing regression of the disease state.

SYNTHESIS

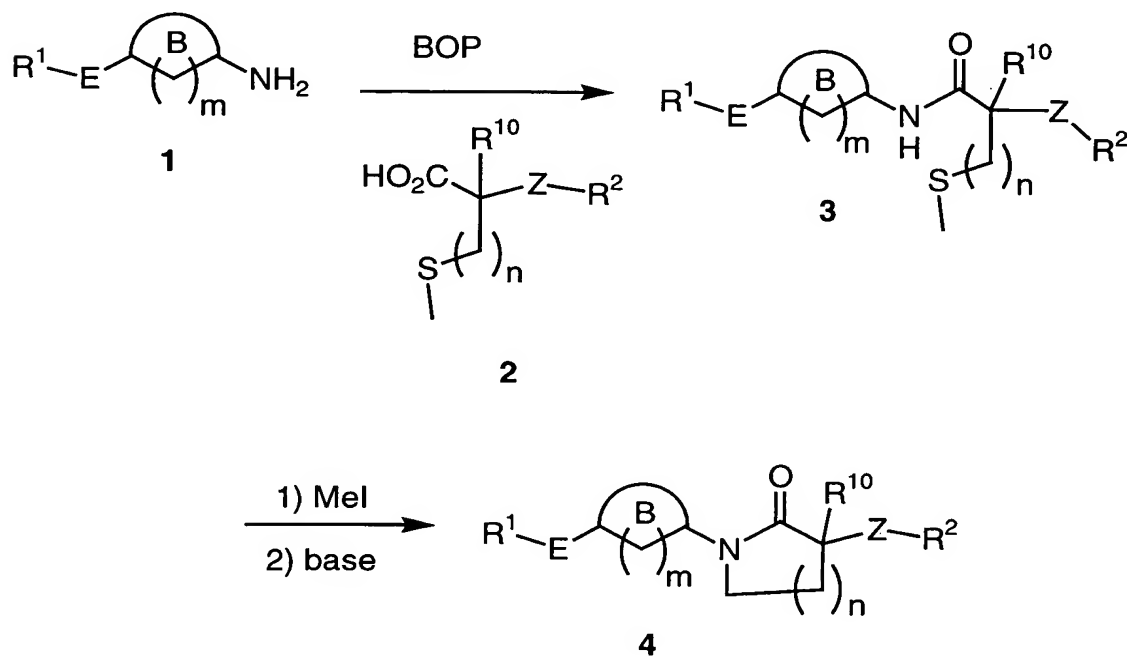
The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. All references cited herein are hereby incorporated in their entirety herein by reference.

The novel compounds of this invention may be prepared using the reactions and techniques described in this section. The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and work up procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Such restrictions to the substituents which are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in

order to obtain a desired compound of the invention. It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. An authoritative account describing the many alternatives to the trained practitioner is Greene and Wuts (*Protective Groups In Organic Synthesis*, Wiley and Sons, 1999).

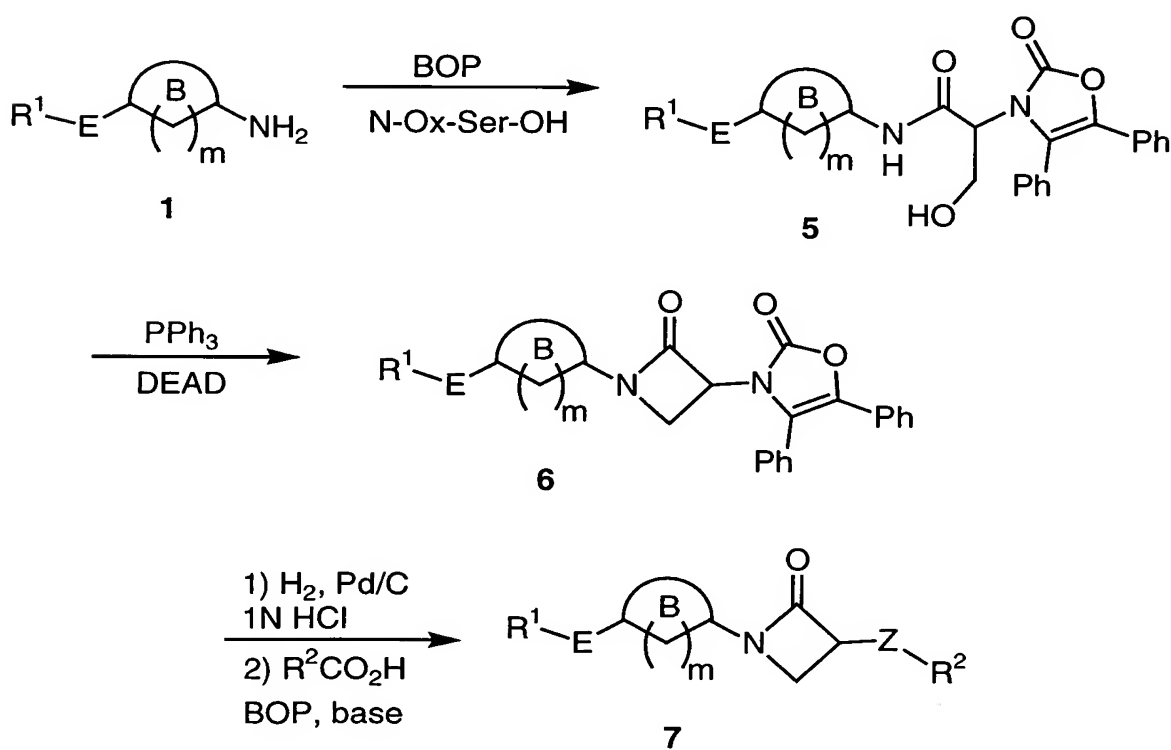
A series of compounds of formula 4 can be synthesized as shown in Scheme 1. Many cyclic amines 1 are available (Cherney, R. J. PCT 02/060859 and PCT 03/075853; and in U.S. Patent Application No. 60/362,604, filed March 8, 2002, both of which are hereby incorporated by reference) and can be coupled to acid 2. The resulting amide 3 can be cyclized (Freidinger et al., *J. Org. Chem.* **1982**, 47, 104) via the activated thioether to the desired lactam 4.

Scheme 1



A series of compounds of formula **7** can be synthesized as shown in Scheme 2. The cyclic amine **1** can be coupled to an appropriate carboxylate to afford amide **5**. This material can be cyclized under Mitsunobu conditions to afford β -lactam **6** (Townsend et al., *J. Amer. Chem. Soc.* **1990**, 112, 760). The protecting group can be removed and an appropriate group can be installed (through coupling or another methodology) to deliver the desired target **7**.

Scheme 2



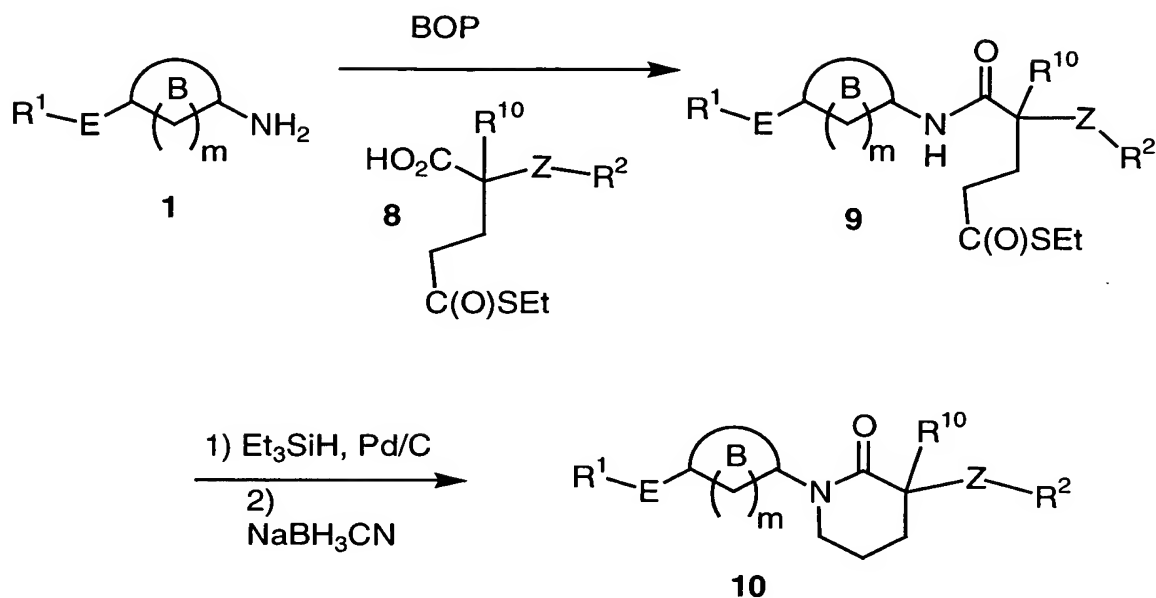
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A series of compounds of formula **10** can be synthesized by the methods shown in Scheme 3. Amine **1** can be coupled to an appropriate carboxylate **8**. The

resulting amide **9** can be cyclized via the aldehyde to afford the target **10**.

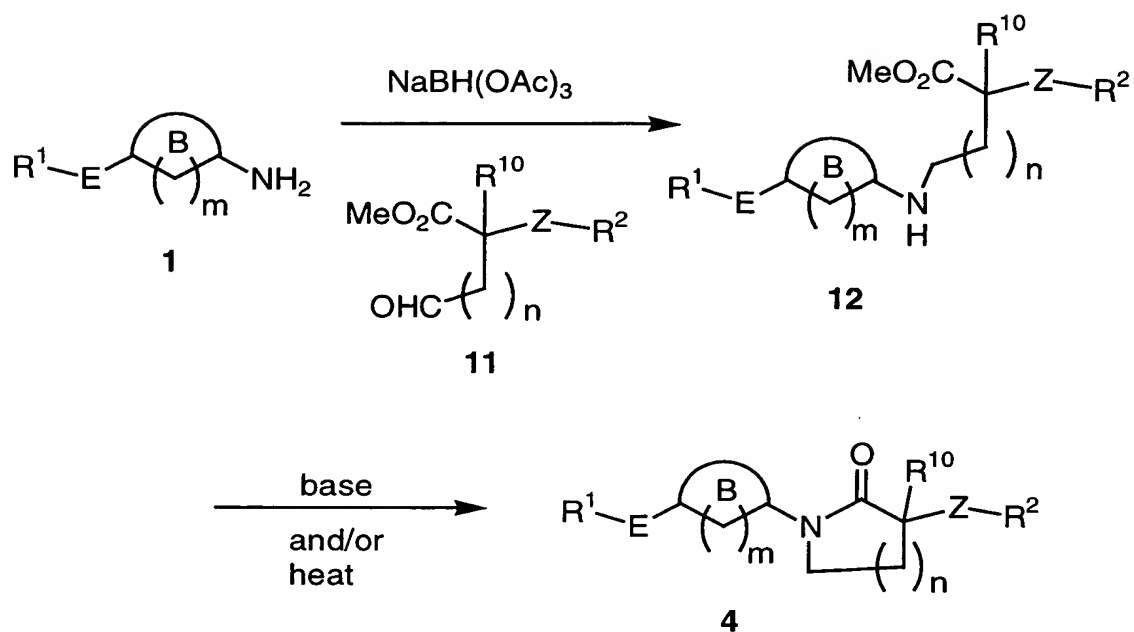
Scheme 3

5



A series of compounds of formula **4** can also be synthesized as shown in Scheme 4. Amine **1** can be converted into **12** via a reductive amination. The secondary amine **12** can be cyclized under a variety of conditions to give the target **4**.

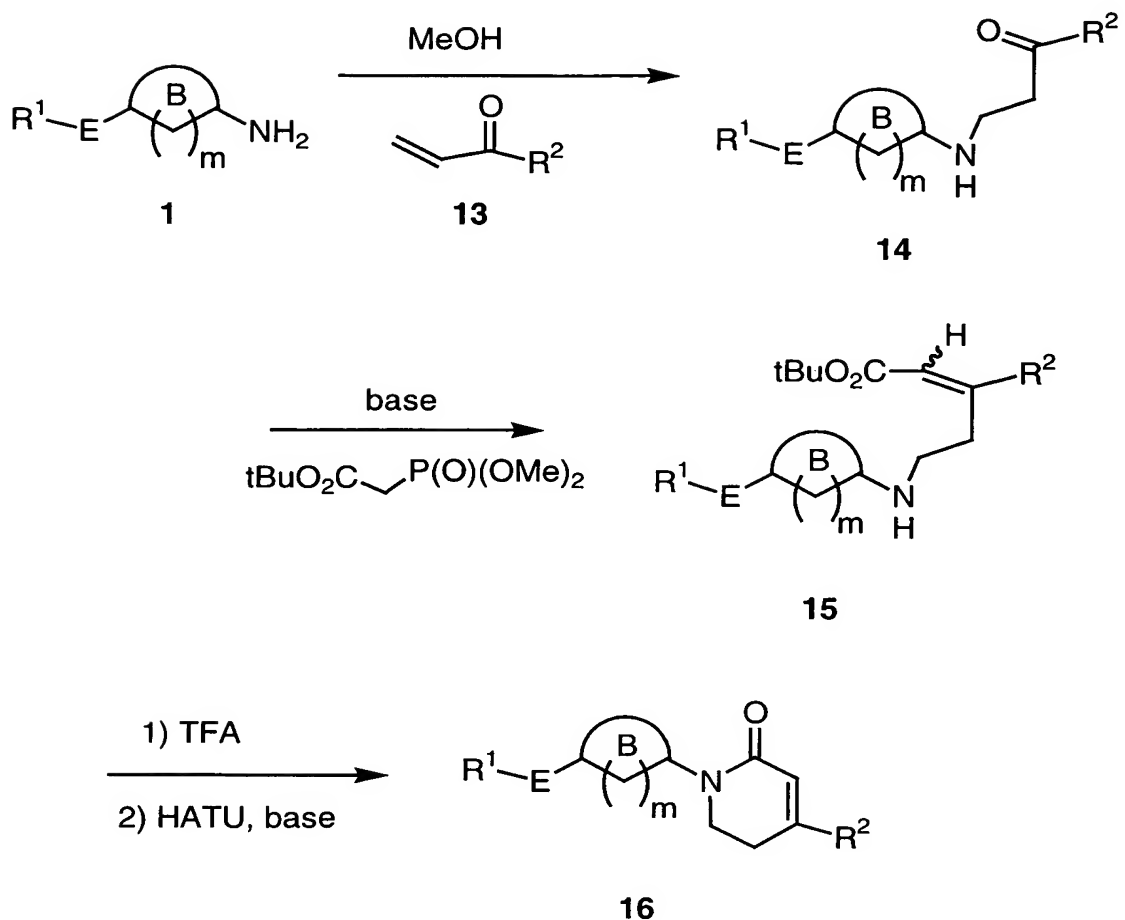
Scheme 4



5

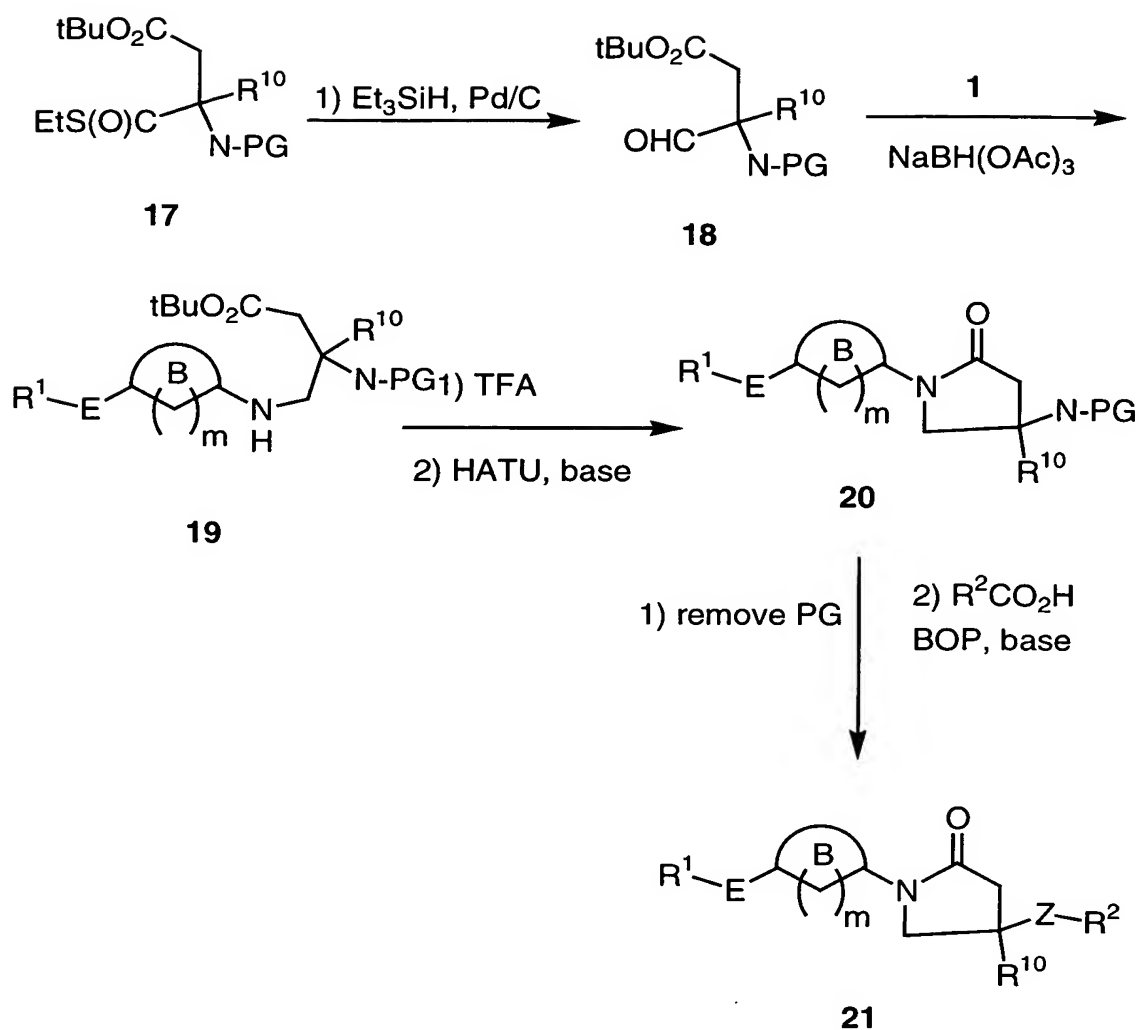
A series of compounds of formula **16** can be synthesized as shown in Scheme 5. Amine **1** can be converted into **14** via a Michael reaction. Treatment of **14** with a phosphonate and base affords **15**. This material can be cyclized through the carboxylate to give **16**.

Scheme 5



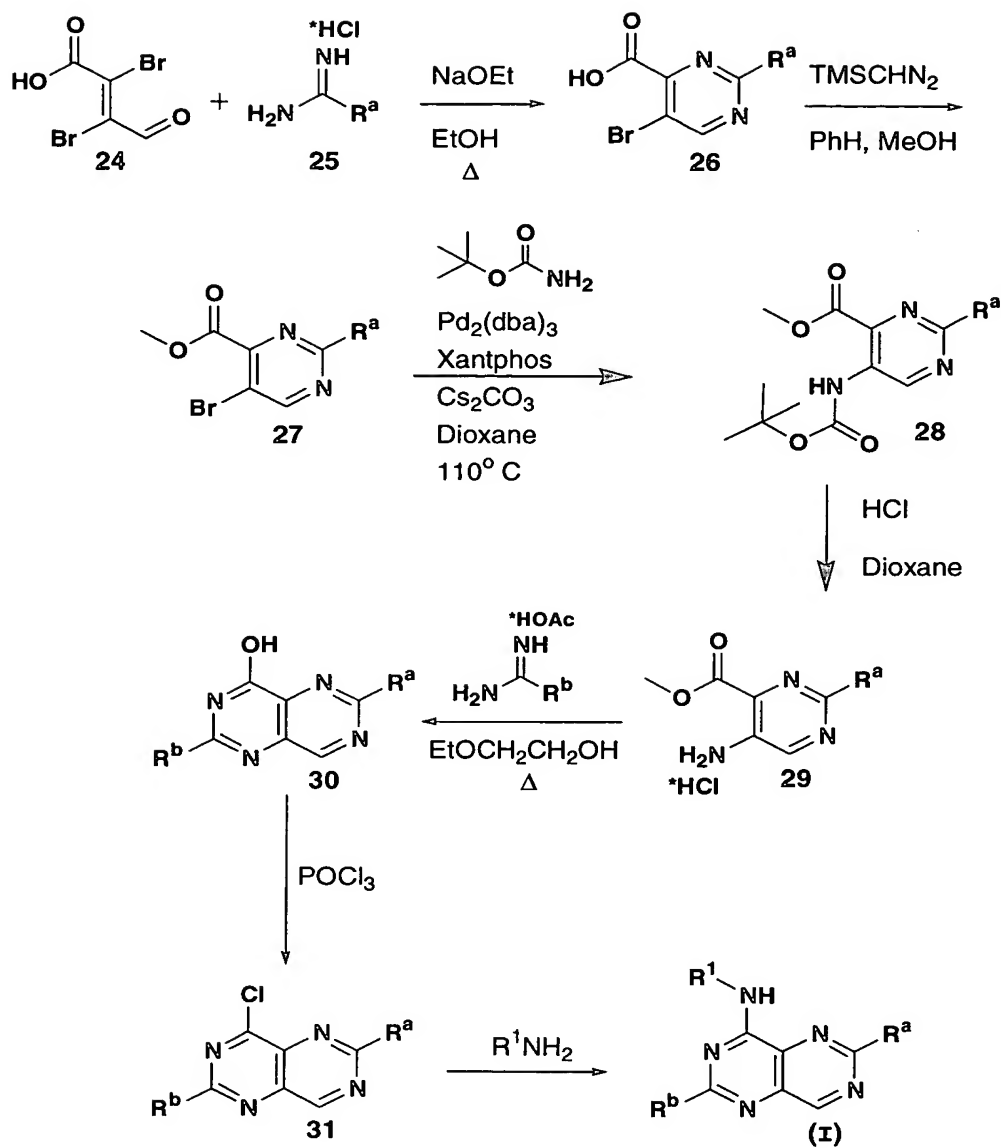
A series of compounds of formula **21** can be synthesized as shown in Scheme 6. The appropriate thioester **17** can be converted into the aldehyde **18**. Reductive amination of **1** with **18** gives the secondary amine **19**. This material can be cyclized through the carboxylate to give **20**. The protecting group can be removed and an appropriate R² group can be coupled to afford target **21**.

Scheme 6



The synthesis of $\text{R}^2 = \text{pyrimido}[5,4\text{-d}]\text{pyrimidin-4-yl}$ is shown in Scheme 7.

Scheme 7.



Intermediates such as **27** can be saponified and coupled to **20** where PG = H₂. The bromine can also be removed via hydrogenation, or used in Suzuki-type
 5 couplings for further elaboration. The conversion of **27** to **28** is performed by the method of Buchwald and Yin, *J. Am. Chem. Soc.*, (124), 6043, 2002.

The synthesis of R² = quinazolines and their analogs wherein the benzene moiety can also be replaced by a
 10 heterocycle are made by the procedures illustrated in Schemes 8 and 8a. Note that for clarity, benzoic acids

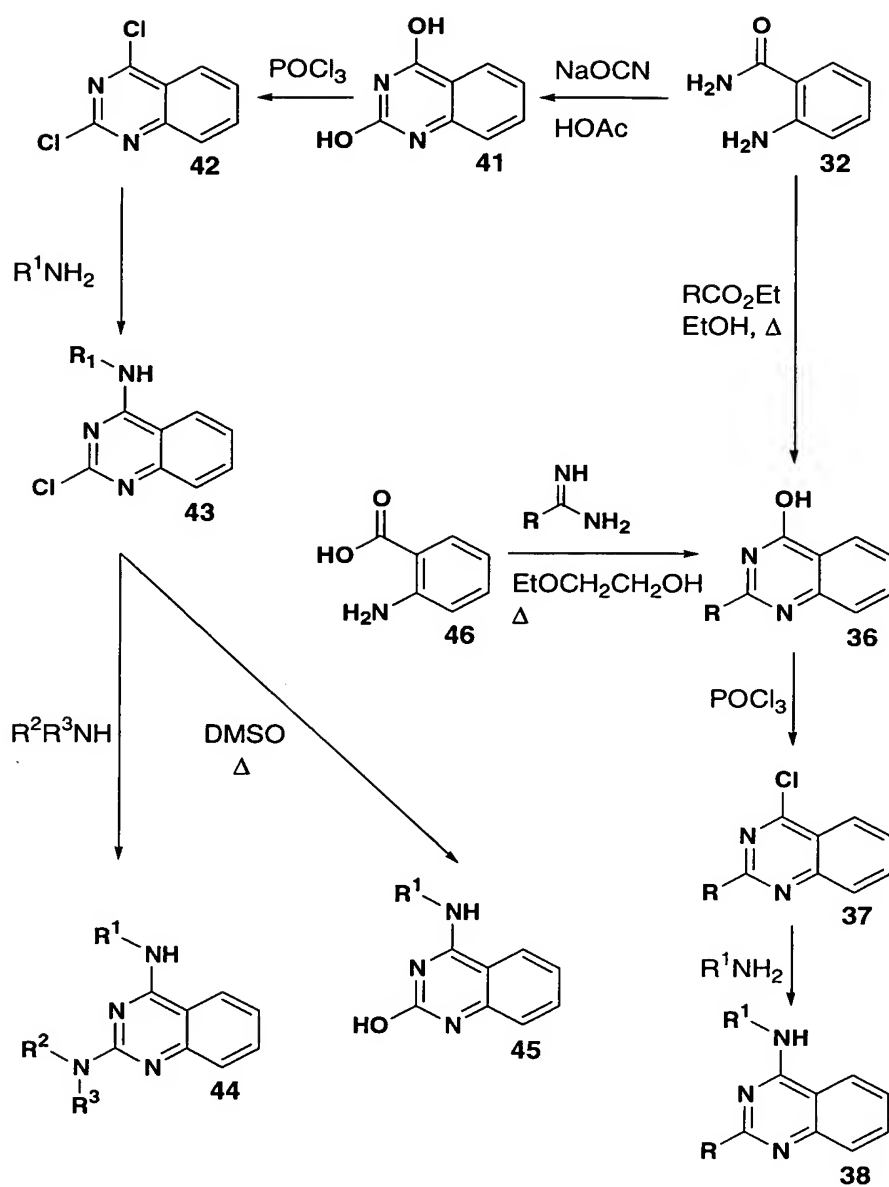
and derivatives were drawn. However, it is to be understood that the benzene ring can be replaced with heterocycles. R^1 in Schemes 8 and 8a represents everything to the left of Z in formula (I) where Z = NH.

5 R^2 and R^3 are the usual substituents found on amines such as H, alkyl, etc., familiar to one skilled in the art and within the scope of R^{7a} in this application.

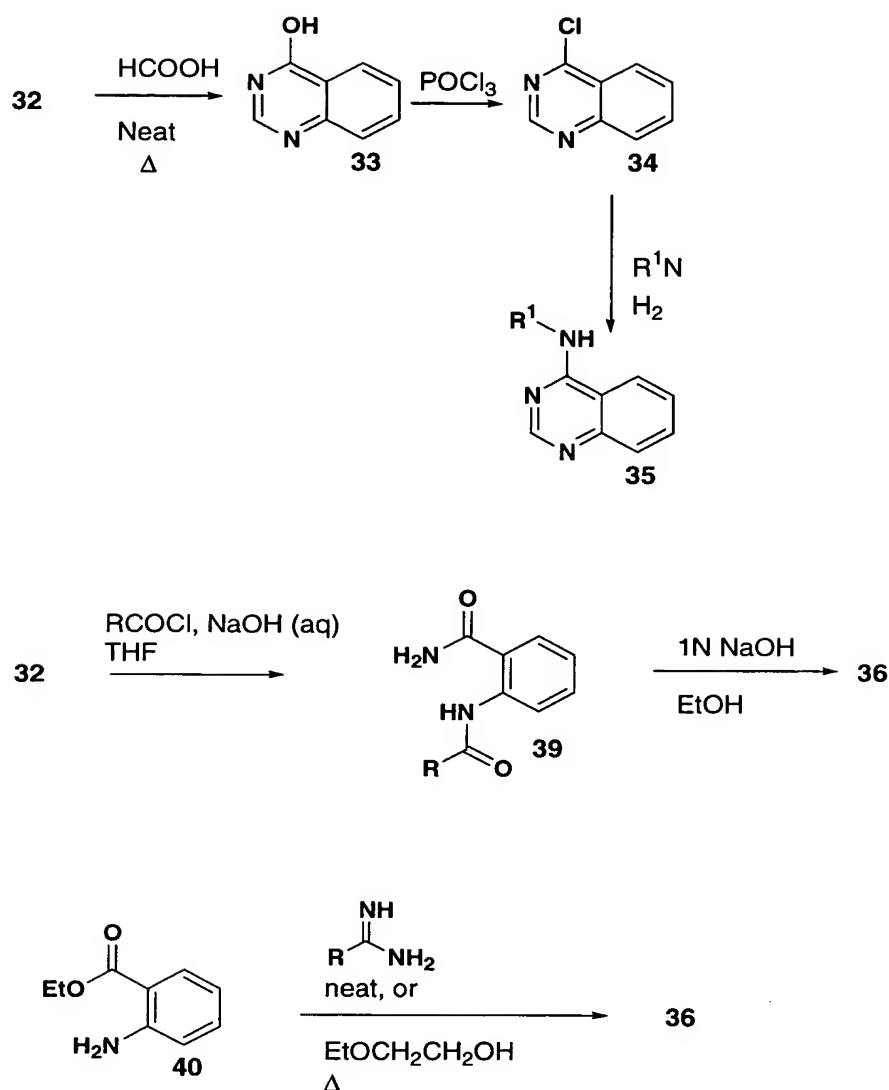
Substituted anthranilic acids in Scheme 8 can be synthesized from BOC-protected anilines via ortho-

10 directed metallation followed by quenching with CO_2 . Bromo or iodo substituted quinazolines in Schemes 8 and 8a can undergo Suzuki-type couplings for further elaboration.

Scheme 8

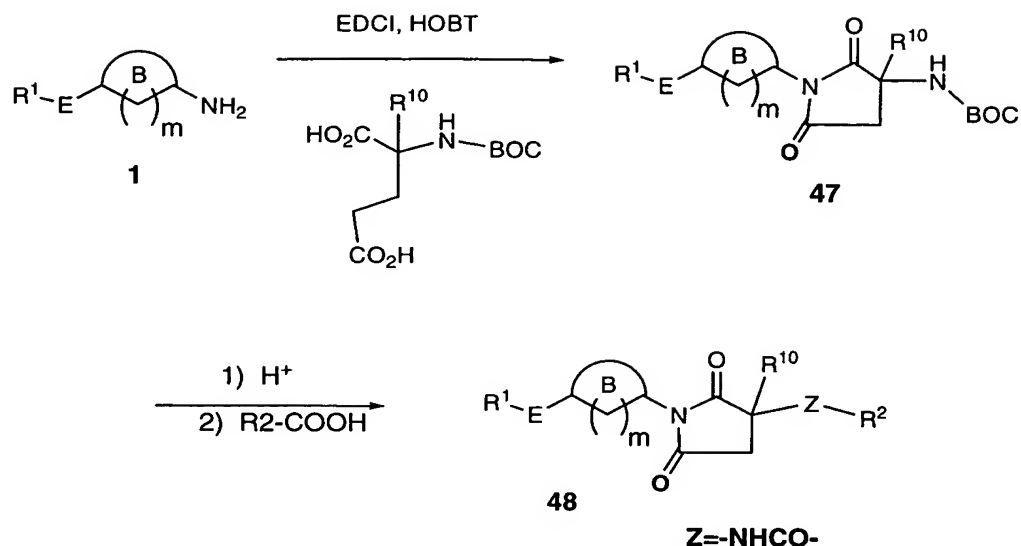


Scheme 8a



Compounds containing a succinimide linker can be synthesized by the methods shown in Scheme 9. Amine **1** is coupled to a protected aspartic acid derivative to yield succinimide **47** which can be deprotected and coupled to a carboxylic acid by the usual means familiar to one skilled in the art to yield the compounds of this invention, **48**.

Schem 9

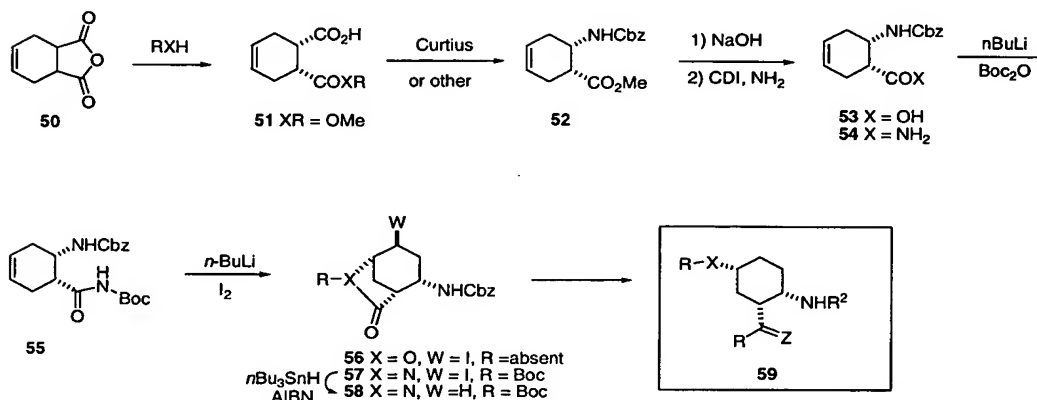


Many core rings **1** have been described (see Cherney PTC WO/03075853 and others above). Others can be synthesized from anhydride openings or the corresponding amino esters (**52**) or acid esters (**51**) as shown in Scheme 10. As described (see Bolm et al. *J. Org. Chem.* **2000**, 65, 6984), anhydride **50** can be opened to the acid ester **51**. A Curtius reaction, or another rearrangement, on the carboxylate of **51** can provide the carbamate **52**.

Hydrolysis of the ester gives the acid **53** which can be converted to the primary amide **54**. This primary amide **54** can be converted in one pot to the bicyclic **57** (through the intermediate **55**) or transformed in a discrete step to acyl carbamate **55** and cyclized with the use of many different electrophiles and bases (see Taguchi et al. *J. Org. Chem.* **1997**, 62, 7330) to give the bicyclic **57**. The carboxylate **53** can also undergo cyclizations to the lactone **56**. These compounds (**56**, **57**, **58**) serve as versatile intermediates because they can be opened in many ways to give substituted rings **59**. These

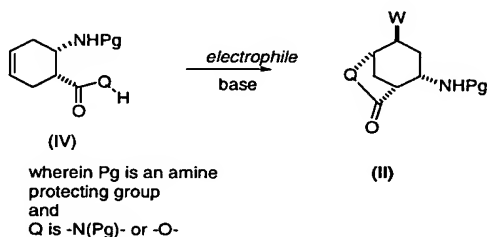
substituted rings **59** can then be incorporated into Schemes 1, 2, 3, 4, 5, 6, and 9 acting as compound **1**.

Scheme 10



More generally, compounds 55-58 may be prepared as described in Scheme 10a. Compounds of Formula (IV), wherein an amine protecting group is as described above, are converted into compounds of Formula (II) by way of an electrophile and base in a suitable solvent.

Scheme 10a



Suitable solvents for the reaction are generally the ether solvents or non reactive hydrocarbon solvents as described above, or mixtures thereof. In particular, the solvents are selected from THF, toluene, and mixtures thereof. Additional non-reactive solvents such as other aromatic solvents (e.g., benzene, anisole, or quinoline) can also be used.

Suitable electrophiles for the reaction include, but are not limited to, iodine, bromine, N-bromosuccinimide,

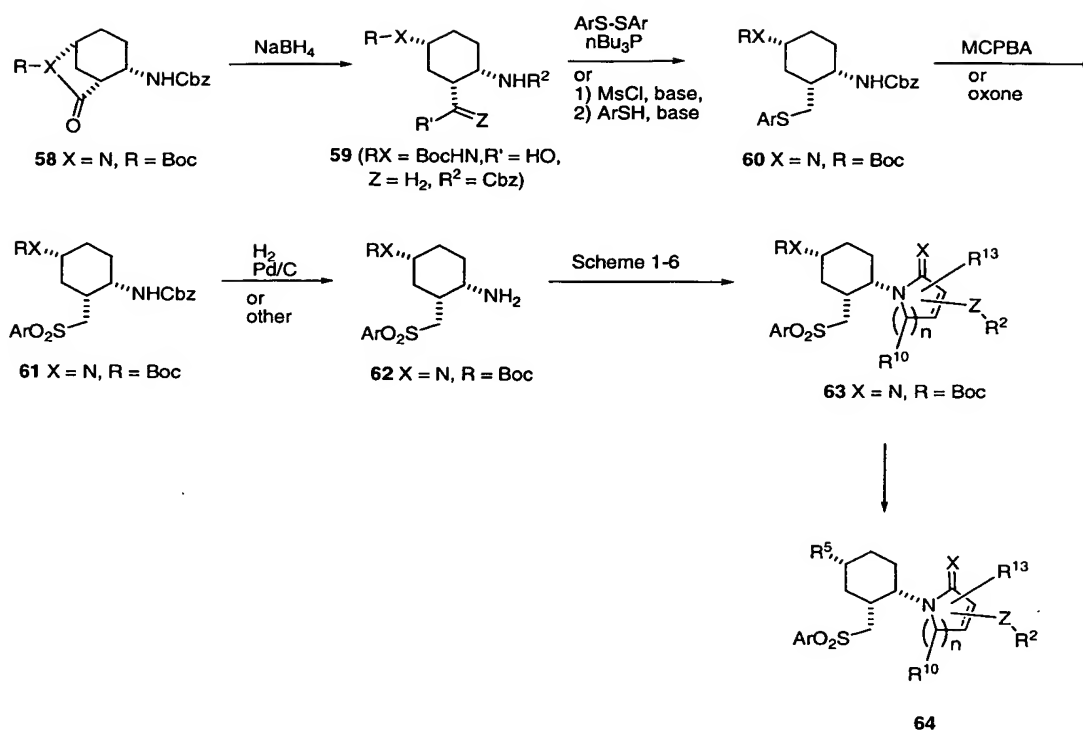
N-iodosuccinimide, N-(phenylseleno)phthalimide, and benzenesulfonyl chloride. Suitable bases for the reaction include, but are not limited to, alkyl lithium such as n-butyl lithium, lithium diisopropylamide (LDA),
5 sodium hydride, lithium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide, sodium bis(trimethylsilyl)amide, Li-Al(O-tButyl)₄.

The reaction may be run at temperatures from about -22° C to about room temperature and alternatively, from
10 about 0° C to about room temperature.

The amine protecting group includes all of those defined above and each may be selected independently to allow for differential removal of the protecting groups from the amine.

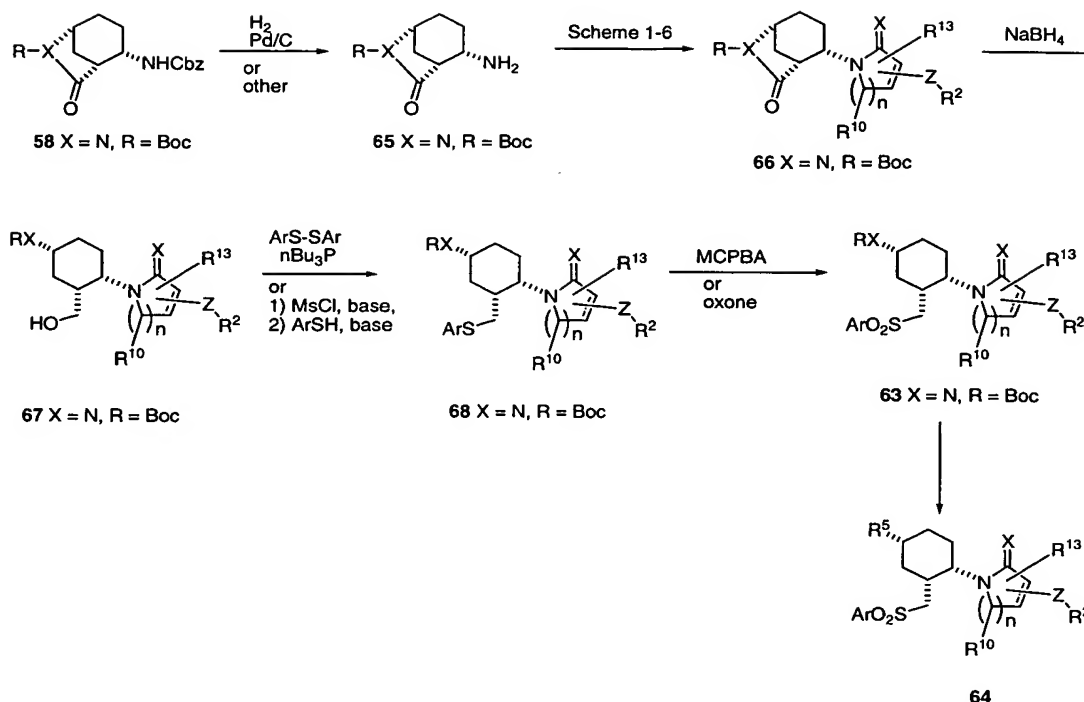
15 Scheme 11 shows how compounds like **59** can be converted into the final compounds of interest. A compound like **58** can be reductively opened to compound **59** (RX = BocHN, R' = HO, Z = H₂, R² = Cbz). Treatment of **59** with Mitsunobu-like conditions (ArSSAr and nBu₃P, wherein
20 Ar may be any of the substituents described by R¹ in the claims) or substitution conditions yields compound **60**. This can be oxidized a number of ways to give the sulfone **61**. Removal of the benzyl carbamate gives the primary amine **62**. This can be incorporated into one of the
25 Schemes 1-6 to afford **63**. The Boc carbamate can then be removed, and the primary amine can be substituted in a variety of ways to the desired final compound **64**.

Scheme 11



In a similar way, Scheme 12 shows how a compound like **58** can be converted into a final compound of interest by changing the order of Scheme 11. The benzyl carbamate of **58** can be removed to give the primary amine **65**. This can be incorporated into one of the Schemes 1-6 to afford **66**. The reductive opening of **66** gives **67**. Treatment of **67** with Mitsunobu-like conditions (ArSSAr and nBu₃P) or substitution conditions yields compound **68**, which can be oxidized to the same compound **63** as above.

Scheme 12



The variables described in the schemes may be the same or different than those described in the claims.

5 They are not meant to limit the claims.

When required, separation of the racemic material can be achieved by HPLC using a chiral column or by a resolution using a resolving agent such as camphonic chloride as in Steven D. Young, et al, *Antimicrobial Agents and Chemotherapy*, **1995**, 2602-2605.

Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments which are given for illustration of the invention and are not intended to be limiting thereof.

15

Examples

Abbreviations used in the Examples are defined as follows: "1 x" for once, "2 x" for twice, "3 x" for thrice, "°C" for degrees Celsius, "g" for gram or grams, "mg" for milligram or milligrams, "mL" for milliliter or

20

milliliters, "¹H" for proton, "h" for hour or hours, "M" for molar, "min" for minute or minutes, "MHz" for megahertz, "MS" for mass spectroscopy, "NMR" for nuclear magnetic resonance spectroscopy, "rt" for room temperature, "tlc" for thin layer chromatography, "EtOAc" for ethyl acetate, "v/v" for volume to volume ratio, "aq" for aqueous solutions. "R" and "S" are stereochemical designations familiar to those skilled in the art. Compound names are provided by the program ChemDraw Ultra (6.0).

Example 1

2-((3S)-1-[(1,2-cis)-2-(4-Methylsulfanyl-benzoylamino)-cyclohexyl]-2-oxo-pyrrolidin-3-ylcarbamoyl)-4-trifluoromethyl-phenyl)-carbamic acid tert-butyl ester

(1a) Cis(±)-(2-amino-cyclohexyl)-carbamic acid benzyl ester trifluoroacetic acid salt (620 mg) (Cherney, R. J. PCT Int Appl.(2000), WO 0260859) was dissolved in DMF (6 mL) prior to the addition of 4-methylmorpholine (0.56 mL) and N-Boc-L-Met-OH (512.0 mg). After cooling to 0 °C, BOP Reagent (907.1 mg) was added. The resulting mixture was warmed to rt and was stirred overnight. EtOAc was added along with 1 N HCl solution. The EtOAc layer was washed with 1 N HCl (aq), NaHCO₃ solution (aq), and brine. The EtOAc was dried (MgSO₄), filtered, and concentrated. Flash chromatography of the resulting residue gave an inseparable mixture of diastereomers cis-[2-(2(S)-tert-butoxycarbonylamino-4-methylsulfanyl-butrylamino)-cyclohexyl]-carbamic acid benzyl ester (921 mg) which was taken forward. MS found: (M + Na)⁺ = 502.4.

(1b) A portion (910 mg) of the above derivative (1a) was dissolved in MeI (12 mL). After stirring overnight at rt, the solution was concentrated and dried. The resulting material was dissolved in DMF (15 mL) and CH₂Cl₂ (15 mL) and cooled to 0 °C prior to the addition of 60% NaH (258.4 mg). After stirring 3 h at rt, EtOAc and brine were added. The EtOAc layer was washed with brine, dried (MgSO₄), filtered, and concentrated. Flash chromatography of the resulting residue gave the mixture of diastereomers cis-[1-(2-benzyloxycarbonylamino-cyclohexyl)-2-oxo-pyrrolidin-3(S)-yl]-carbamic acid benzyl ester (358 mg). MS found: (M + Na)⁺ = 454.4.

(1c) A portion (340 mg) of the above derivative (1b) was dissolved in CH₂Cl₂ (2 mL) and cooled to 0 °C prior to the addition of TFA. After 1 h at rt, the mixture was concentrated. A portion (270 mg) of the resulting residue was dissolved in DMF (5 mL) prior to the addition of 4-methylmorpholine (0.24 mL) and 2-(tert-butoxycarbonyl)amino-5-trifluoromethylbenzoic acid (220 mg) (Takagishi et al., *Synlett* **1992**, 360). After cooling to 0 °C, BOP Reagent (322 mg) was added. The resulting mixture was warmed to rt and was stirred overnight. EtOAc was added along with 1 N HCl solution. The EtOAc layer was washed with 1 N HCl (aq), NaHCO₃ solution (aq), and brine. The EtOAc was dried (MgSO₄), filtered, and concentrated. Flash chromatography of the resulting residue gave the mixture of diastereomers cis-{2-[1-(2-benzyloxycarbonylamino-cyclohexyl)-2-oxo-pyrrolidin-3(S)-yl]carbamoyl]-4-trifluoromethyl-phenyl}-carbamic acid tert-butyl ester (196 mg). MS found: (M + Na)⁺ = 641.4.

- (1d) A portion (180 mg) of the above derivative (1c) was dissolved in MeOH prior to the addition of 10% Pd/C (40 mg). A hydrogen balloon was added and the mixture was stirred for 3 h. The Pd/C was filtered off and the solvent was concentrated to a mixture of diastereomers
- 5 cis-{2-[1-(2-amino-cyclohexyl)-2-oxo-pyrrolidin-3(S)-ylcarbamoyl]-4-trifluoromethyl-phenyl}-carbamic acid tert-butyl ester (140 mg). MS found: (M + H)⁺ = 485.4.
- 10 (1e) A portion (70 mg) of the above derivative (1d) was dissolved in DMF (5 mL) prior to the addition of 4-methylmorpholine (0.05 mL) and 4-(methylthio)benzoic acid (52 mg). After cooling to 0 °C, BOP Reagent (77 mg) was added. The resulting mixture was warmed to rt and was
- 15 stirred overnight. EtOAc was added along with 1 N HCl solution. The EtOAc layer was washed with 1 N HCl (aq), NaHCO₃ solution (aq), and brine. The EtOAc was dried (MgSO₄), filtered, and concentrated. Flash chromatography of the resulting residue gave the title mixture of
- 20 diastereomers (76 mg). MS found: (M + H)⁺ = 635.4.

Example 2

- 25 2-((3S)-1-[(1,2-cis)2-(4-Methylsulfanyl-benzoylamino)-cyclohexyl]-2-oxo-pyrrolidin-3-ylcarbamoyl)-4-trifluoromethyl-phenyl)-amino

- (2a) A portion (19 mg) of the above Example 1 was dissolved in CH₂Cl₂ (2 mL) and cooled to 0 °C prior to the addition of TFA. After 1 h at rt, the mixture was
- 30 concentrated and dried. This gave the title compound (17 mg). MS found: (M + H)⁺ = 535.4.

Example 3

N-((3S)-1-[(1S,2R,4R)-(Isopropyl-methyl-amino)-2-(toluene-4-sulfonylmethyl)-cyclohexyl]-2-oxo-pyrrolidin-3-yl)-3
-trifluoromethyl-benzamide

(3a) 1,4-Cyclohexanedione mono-ethylene ketal (25 g) was dissolved in THF and cooled to -78 °C. 1M Lithium bis(trimethylsilyl)amide (160 mL) in THF was added dropwise. After 30 min, ethyl cyanoformate (15.9 mL) was added dropwise. After 60 min, the solution was poured into EtOAc and water containing ice. The organic layer was washed with water and brine before it was dried and concentrated. This crude was filtered through a plug of silica to give the 8-oxo-1,4-dioxo-spiro[4.5]decane-7-carboxylic acid ethyl ester (32.4 g). MS found: (M + H)⁺ = 228.9

(3b) The above derivative (3a) (36.5 g) was dissolved in toluene (500 mL) prior to the addition of (S)-methylbenzyl amine (23 mL) and ytterbium (III) triflate (0.37 g). This mixture was stirred at reflux for 3 h. After cooling to rt overnight, the solvent was removed to a golden oil. This oil was dissolved in acetonitrile (420 mL) prior to the addition of acetic acid (100 mL) and NaBH(OAc)₃ (67.8 g). The mixture was stirred for 5 days at rt. The solvent was removed before being redissolved in CH₂Cl₂. After cooling in an ice bath, 1N NaOH was added (pH = 8). The organic layer was washed with brine, dried, filtered, and concentrated. Flash chromatography of the resulting residue gave 8(S)-(1(S)-phenyl-ethylamino)-1,4-dioxo-spiro[4.5]decane-7(R)-

carboxylic acid ethyl ester (26.2 g): ^1H NMR (CDCl_3 , δ ppm, 300 MHz) 1.31 (m, 6H), 1.46 (m, 1H), 1.6-1.84 (m, 4H), 2.1 (t, 1H), 2.85 (m, 1H), 3.16 (m, 1H), 3.76 (m, 1H), 3.93 (m, 4H), 4.19 (q, 2H), 7.2-7.4 (m, 5H).

5

(3c) The above derivative (3b) (16.3 g) was dissolved in Et_2O (160 mL) and cooled to 0 °C. 1M Lithium aluminum hydride in THF (117.3 mL) was added dropwise. After the addition, the solution was stirred for 2 hr at 0 °C. The
10 reaction was quenched with water (4.4 mL) and then 1N NaOH (17.6 mL). The solids were filtered off through a pad of celite. The filtrate was concentrated to an oil. This material was dissolved in MeOH (20 mL) prior to the addition of 20% $\text{Pd}(\text{OH})_2$ (3 g). This solution was placed
15 on a Parr apparatus at 50 psi. The solution was mixed overnight. The palladium was filtered off and the solution was concentrated. The resulting oil was dissolved in THF (160 mL) and water (20 mL) prior to the addition of triethylamine (8.8 mL). After cooling to 0
20 °C, dibenzyl dicarbonate (18.2 g) was added. The solution was warmed to rt and was stirred overnight. Ethyl acetate was added along with brine. The organic layer was washed with brine, dried, filtered, and concentrated. Flash chromatography of the resulting residue gave
25 (7R,8S)-(7-hydroxymethyl-1,4-dioxaspiro[4.5]dec-8-yl)-carbamic acid benzyl ester (9.8 g). MS found: $(\text{M} + \text{H})^+ = 322.2$.

(3d) A portion (100 mg) of the above derivative (3c) was
30 dissolved in THF (10 mL) prior to the addition of tri-*n*-butylphosphine (0.86 mL). 4-Bromophenyl disulfide (233 mg) was added and the solution was stirred in a 75 °C oil

bath. After 5 h, the reaction was cooled to rt and flash chromatography gave (7R,8S)-[7-(4-bromophenylsulfanylmethyl)-1,4-dioxaspiro[4.5]dec-8-yl]-carbamic acid benzyl ester (137 mg). ^1H NMR (CDCl_3 , δ)
5 ppm, 300 MHz) 1.39 (t, 1H), 1.5-1.9 (m, 9H), 2.05 (m, 1H), 2.73 (m, 1H), 3.0 (dd, 1H), 3.93 (m, 4H), 4.08 (m, 1H), 4.9 (br d, 1H), 5.1 (s, 2H), 7.17 (d, 2H), 7.36 (m, 7H).

10 (3e) A portion (2.5 g) of the above derivative (3d) was dissolved in CH_2Cl_2 (100 mL) and cooled to 0 °C prior to the addition 65% *m*-CPBA (3.1 g). After 2 h, the solution was washed with saturated NaHCO_3 solution, brine
15 solution, dried, filtered, and concentrated. Flash chromatography of the resulting residue gave (7R, 8S)-[7-(4-bromo-benzenesulfonylmethyl)-1,4-dioxaspiro[4.5]dec-8-yl]-carbamic acid benzyl ester (2.59 g). MS found: $(\text{M} + \text{H})^+ = 525.9$.

20 (3f) A portion (2.1 g) of the above derivative (3e) was dissolved in DMF (10 mL) prior to the addition of $\text{PdCl}_2(\text{PPh}_3)_2$ (56 mg) and $\text{Sn}(\text{Me})_4$ (0.8 mL). The resulting solution was heated in an oil bath at 80 °C. Four
25 addition portions of $\text{Sn}(\text{Me})_4$ (0.8 mL each) were added over 3 days. After cooling, EtOAc and brine were added. The organic layer was washed with brine, dried, filtered, and concentrated. Flash chromatography of the resulting
30 residue gave (7R, 8S)-([7-(toluene-4-sulfonylmethyl)-1,4-dioxaspiro[4.5]dec-8-yl]-carbamic acid benzyl ester (1.0 g). MS found: $(\text{M} + \text{H})^+ = 460.3$.

(3g) A portion (1.0 g) of the above derivative (3f) was dissolved in MeOH prior to the addition of 10% Pd/C (120 mg). A hydrogen balloon was added and the mixture was stirred for 1.5 h. The Pd/C was filtered off and the
5 solvent was concentrated to (7R, 8S)-7-(toluene-4-sulfonylmethyl)-1,4-dioxo-spiro[4.5]dec-8-ylamine (740 mg). MS found: $(M + H)^+ = 326.3$.

(3h) A portion (730 mg) of the above derivative (3g) was
10 dissolved in DMF prior to the addition of 4-methylmorpholine (0.74 mL) and N-Cbz-L-Met-OH (889.8 mg). After cooling to 0 °C, BOP Reagent (1.4 g) was added. The resulting mixture was warmed to rt and was stirred overnight. EtOAc was added along with 1 N HCl solution.
15 The EtOAc layer was washed with 1 N HCl (aq), NaHCO₃ solution (aq), and brine. The EtOAc was dried (MgSO₄), filtered, and concentrated. Flash chromatography of the resulting residue gave {(1S)3-methylsulfanyl-1-[(7R,8S)-7-(toluene-4-sulfonylmethyl)-1,4-dioxo-spiro[4.5]dec-8-ylcarbamoyl]-propyl}-carbamic acid benzyl ester (1.1 g).
20 MS found: $(M + Na)^+ = 613.4$.

(3i) A portion (330 mg) of the above derivative (3h) was dissolved in MeI (6 mL). After stirring overnight at rt,
25 the solution was concentrated and dried. A portion (50 mg) of the resulting material was dissolved in DMF (1.5 mL) prior to the addition of Cs₂CO₃ (133 mg). After stirring overnight at rt, EtOAc and brine were added. The EtOAc layer was washed with brine, dried (MgSO₄),
30 filtered, and concentrated. Flash chromatography of the resulting residue gave {(3S)-2-oxo-1-[(7R,8S)-7-(toluene-4-sulfonylmethyl)-1,4-dioxo-spiro[4.5]dec-8-yl]-

pyrrolidin-3-yl}-carbamic acid benzyl ester (19 mg). MS found: $(M + Na)^+ = 565.3$.

(3j) A portion (580 mg) of the above derivative (3i) was
5 dissolved in CH_3CN (10 mL) prior to the addition of 1N
HCl (10 mL). The mixture was stirred in a 60 °C oil bath
for 4 h. After cooling the solution was concentrated.
Flash chromatography of the resulting residue gave {(3S)-
2-oxo-1-[(1S,2R)-4-oxo-2-(toluene-4-sulfonylmethyl)-
10 cyclohexyl]-pyrrolidin-3-yl}-carbamic acid benzyl ester
(270 mg). MS found: $(M + Na)^+ = 521.2$.

(3k) The above derivative (3j) (270 mg) was dissolved in
Ti(OiPr)₄ (4 mL) prior to the addition of isopropylamine
15 (0.4 mL). After 1.5 h, MeOH (7 mL) was added followed by
NaBH₄ (57 mg). After 1 h, the reaction was quenched by
the addition of 0.1N NaOH and filtered through celite.
The filtrate was concentrated to a mixture of
diastereomers. Flash chromatography of the resulting
20 mixture gave two diastereomers: {(3S)-1-[(1S,2R,4R)-
isopropylamino-2-(toluene-4-sulfonylmethyl)-cyclohexyl]-
2-oxo-pyrrolidin-3-yl}-carbamic acid benzyl ester (3ka)
(59 mg), MS found: $(M + H)^+ = 542.3$; and {(3S)-1-
[(1S,2R,4S)-isopropylamino-2-(toluene-4-sulfonylmethyl)-
25 cyclohexyl]-2-oxo-pyrrolidin-3-yl}-carbamic acid benzyl
ester (3kb) (28 mg), MS found: $(M + H)^+ = 542.4$.

(3l) The above derivative (3ka) (57 mg) was dissolved in
MeOH (1.3 mL) prior to the addition of 37% formaldehyde
30 in water (53 mg). After 1.5 h, NaBH₃CN (10.4 mg) was
added. After 1 h, saturated NaHCO₃ was added and some of
the MeOH was removed. EtOAc was added and the organic

layer was washed with brine, dried, filtered, and concentrated. The resulting residue was dissolved in MeOH prior to the addition of 5% Pd/BaSO₄ (100 mg). A hydrogen balloon was added and the mixture was stirred.

5 Two more portions (50 mg each) of 5% Pd/BaSO₄ were added. The reaction was stirred for a total of 8 h. The Pd/BaSO₄ was filtered off and the solvent was concentrated. The resulting residue was dissolved in DMF prior to the addition of 4-methylmorpholine (34 mg) and

10 3-trifluoromethyl-benzoic acid (32 mg). After cooling to 0 °C, HATU (64 mg) was added. The resulting mixture was warmed to rt and was stirred overnight. EtOAc was added along with saturated NaHCO₃ solution. The EtOAc layer was washed with NaHCO₃ solution (aq), dried (MgSO₄),

15 filtered, and concentrated. Reverse phase HPLC purification (gradient elution, water/acetonitrile/TFA) of the resulting residue provided the title compound (36 mg). MS found: (M+ H)⁺ = 594.3.

Example 4

20 N-{(3S)-1-[(1S,2R,4S)-(Isopropyl-methyl-amino)-2-(toluene-4-sulfonylmethyl)-cyclohexyl]-2-oxo-pyrrolidin-3-yl}-3-trifluoromethyl-benzamide

25 (4a) Derivative (3kb) (28 mg) was incorporated into Example (31) to give the title compound (8.1 mg). MS found: (M + H)⁺ = 594.3.

Example 5

30 N-{(3S)-1-[(1S,2R,4R)-2-Benzenesulfonylmethyl-(isopropyl-methyl-amino)-cyclohexyl]-2-oxo-pyrrolidin-3-yl}-3-trifluoromethyl-benzamide

(5a) Phenyl disulfide was incorporated into Example 3 - step (3d) and step (3f) was skipped to give two diastereomers. The first diastereomer was the title compound (12.3 mg). MS found: $(M + H)^+ = 580.3$.

5

Example 6

N-{(3S)-1-[(1S,2R,4S)-2-Benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-2-oxo-pyrrolidin-3-yl}-3-trifluoromethyl-benzamide

10

(6a) The second diastereomer from above (5a) was isolated as the title compound. MS found: $(M + H)^+ = 580.3$.

Example 7

15 N-{(3S)-1-[(1S,2R,4R)-2-Benzenesulfonylmethyl-4-(isopropyl-ethyl-amino)-cyclohexyl]-2-oxo-pyrrolidin-3-yl}-3-trifluoromethyl-benzamide

(7a) Acetaldehyde was incorporated into Example 5 (in the analogous step to 3l) to give two diastereomers. The first diastereomer was the title compound (30 mg). MS found: $(M + H)^+ = 594.3$.

20

Example 8

25 N-{(3S)-1-[(1S,2R,4S)-2-Benzenesulfonylmethyl-4-(isopropyl-ethyl-amino)-cyclohexyl]-2-oxo-pyrrolidin-3-yl}-3-trifluoromethyl-benzamide

(8a) The second diastereomer from above (7a) was the title compound (7 mg). MS found: $(M + H)^+ = 594.3$.

30

Example 9

N-{(3S)-1-[(1S,2R,4R)-2-Benzenesulfonylmethyl-4-(isopropyl-cyclopropylmethyl-amino)-cyclohexyl]-2-oxo-pyrrolidin-3-yl}-3-trifluoromethyl-benzamide

5

(9a) Cyclopropanecarboxaldehyde was incorporated into Example 5 (in the analogous step to 3l) to give the title compound (25 mg). MS found: $(M + H)^+ = 620.3$.

10

Example 10

(±) N-{(3S*)-1-[(1S*,2R*,4R*)-4-Azido-2-(4-methylsulfanyl-benzenesulfonylmethyl)-cyclohexyl]-3-methyl-2-oxo-pyrrolidin-3-yl}-3-trifluoromethyl-benzamide

15 (10a) 1-Methanesulfonyl-4-methylsulfanyl-benzene (3.4 g) was dissolved in THF (40 mL) and cooled to -78°C prior to the addition of 1.6 M nBuLi (10.4 mL). After 0.5 h, $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (2.1 mL) was added followed by cis(±)-4-(benzyloxy)-1,2-epoxycyclohexane (2.3 g) (Chini et al. *J. Org. Chem.* 20 **1990**, 55, 4265) in THF (20 mL). After an addition 1 h at -78°C , the solution was warmed to 0°C . After 2 h, the solution was cooled to -78°C and 1N HCl solution (aq) was added. The solution was warmed to rt and EtOAc was added. The organic layer was washed with brine, dried, 25 filtered, and concentrated. Flash chromatography of the resulting residue gave (±)(1R*,2R*,4S*)-4-benzyloxy-2-(4-methylsulfanyl-benzenesulfonylmethyl)-cyclohexanol (2.9 g) as the major product. MS found: $(M + H)^+ = 407.1$.

30 (10b) A portion of the above material (1.9 g) was dissolved in CH_2Cl_2 (15 mL) and cooled to 0°C prior to the addition of Et_3N (2 mL) and methanesulfonyl chloride

(0.55 mL). After 1 h, the CH_2Cl_2 was removed and EtOAc was added. This was washed with 1N HCl, saturated NaHCO_3 , and brine. The organic layer was dried, filtered, and concentrated. This solid was dissolved in
5 DMSO (20 mL) prior to the addition of NaN_3 (2.35 g). This was heated at 80 °C for 18 h. After cooling to 0 °C, water was added and it was extracted with EtOAc. The organic layer was washed with brine, dried, filtered, and concentrated. Flash chromatography of the resulting
10 residue gave (\pm)(1S*,2R*,4S*)-4-benzyloxy-2-(4-methylsulfanyl-benzenesulfonylmethyl)-azidocyclohexane (1.4 g). MS found: $(\text{M} - \text{N}_3)^+ = 388.5$.

(10c) A portion of the above material (1.3 g) was
15 dissolved in CH_2Cl_2 (15 mL) and cooled to -78 °C prior to the addition of 1.0M BCl_3 (3.9 mL) in CH_2Cl_2 . The reaction was stirred at 0 °C for 2 h. After cooling to -78 °C, MeOH (8 mL) was added. The reaction was warmed to 0 °C and then rt. The resulting solution was extracted
20 with CH_2Cl_2 . The organic layer was washed with saturated NaHCO_3 solution (aq), brine, dried, filtered, and concentrated. Flash chromatography of the resulting residue gave (\pm)(1S*,2R*,4S*)-4-hydroxy-2-(4-methylsulfanyl-benzenesulfonylmethyl)-azidocyclohexane
25 (1.1 g). MS found: $(\text{M} - \text{HN}_3)^+ = 298.1$.

(10d) The above material (1.1 g) was dissolved in MeOH (10 mL) prior to the addition of 5% Pd/ BaSO_4 (800 mg). A hydrogen balloon was added and the solution was stirred
30 for 4.0 h. The palladium was filtered off and the solution was concentrated to (\pm)(1S*,2R*,4S*)-4-hydroxy-2-(4-methylsulfanyl-benzenesulfonylmethyl)-

cyclohexylamine: MS found: $(M + H)^+ = 316.2$. The resulting residue was dissolved in THF (10 mL) and water (2 mL) prior to the addition of Et_3N (0.88 mL). This was cooled to 0 °C and Boc_2O (761 mg) was added. The
5 reaction was warmed to rt and was stirred overnight. The reaction was quenched with water and EtOAc. The EtOAc layer was washed with 1 N HCl solution, $NaHCO_3$ solution, and brine. The organic layer was dried, filtered, and concentrated (1.44 g). This material (1.44 g) was
10 dissolved in CH_2Cl_2 (15 mL) and cooled to 0 °C prior to the addition of Et_3N (1.3 mL) and methanesulfonyl chloride (0.37 mL). After 1 h, the CH_2Cl_2 was removed and EtOAc was added. This was washed with 1N HCl, saturated $NaHCO_3$, and brine. The organic layer was dried,
15 filtered, and concentrated. This solid was dissolved in DMSO (10 mL) prior to the addition of NaN_3 (1.03 g). This was heated at 80 °C for 18 h. After cooling to 0 °C, water was added and it was extracted with EtOAc. The organic layer was washed with brine, dried, filtered, and
20 concentrated. Flash chromatography of the resulting residue gave (\pm)(1S*,2R*,4R*)-[4-azido-2-(4-methylsulfanyl-benzenesulfonylmethyl)-cyclohexyl]-carbamic acid tert-butyl ester (1.2 g). MS found: $(M + Na + CH_3CN)^+ = 504.3$.

25
(10e) A portion of the above material (114 mg) was dissolved in CH_2Cl_2 (2 mL) and cooled to 0 °C prior to the addition of TFA (2 mL). After the reaction was warmed to rt over 45 min, it was concentrated and dried. The
30 resulting residue was dissolved in DMF (4 mL) prior to the addition of HATU (166.7 mg) and N-Boc- α -methyl-dl-

Met-OH (101.7 mg). After cooling to 0 °C, diisopropylethylamine (0.74 mL) was added. The resulting mixture was warmed to rt and was stirred overnight before being concentrated. Flash chromatography of the resulting residue gave {1-[4-azido-2-(4-methylsulfanyl-benzenesulfonylmethyl)-cyclohexylcarbamoyl]-1-methyl-3-methylsulfanyl-propyl}-carbamic acid tert-butyl ester (113 mg) as a mixture of diastereomers. MS found: (M + H)⁺ = 586.5.

10

(10f) The above derivative was dissolved in MeI (5 mL). After stirring overnight at rt, the solution was concentrated and dried. The resulting material was dissolved in DMF (4 mL) prior to the addition of Cs₂CO₃ (380 mg). After stirring overnight the solution was filtered and concentrated. Flash chromatography of the resulting residue provided the bottom diastereomer (TLC 80% EtOAc/Hex) (±){(3S*)-1-[(1S*,2R*,4R*)-4-azido-2-(4-methylsulfanyl-benzenesulfonylmethyl)-cyclohexyl]-3-methyl-2-oxo-pyrrolidin-3-yl}-carbamic acid tert-butyl ester (36 mg). MS found: (M + Na)⁺ = 538.5.

20

(10g) The above material was dissolved in CH₂Cl₂ (1 mL) and cooled to 0 °C prior to the addition of TFA (1 mL).

25

After the reaction was warmed to rt over 30 min, it was concentrated and dried. The resulting residue was dissolved in CH₂Cl₂ prior to the addition of diisopropylethylamine (0.05 mL) and 3-

(trifluoromethyl)benzoyl chloride (28 mg). After

30

stirring for 1.5 h, the reaction was diluted with CH₂Cl₂ and washed with water, 10% citric acid solution, NaHCO₃ solution, and brine. The CH₂Cl₂ layer was dried (MgSO₄),

filtered, and concentrated. Flash chromatography of the resulting residue provided the title compound (24 mg).

MS found: $(M + H)^+ = 610.5$.

5

Example 11

(±) N-((3S*)-1-[(1S*,2R*,4R*)-4-Amino-2-(4-methylsulfanyl-benzenesulfonylmethyl)-cyclohexyl]-3-methyl-2-oxo-pyrrolidin-3-yl)-3-trifluoromethyl-benzamide

10 (11a) Example 10 (20 mg) was dissolved in MeOH (2 mL) prior to the addition of 5% Pd/BaSO₄ (10 mg). A hydrogen balloon was added and the mixture was stirred. After stirring 45 min, the Pd/BaSO₄ was filtered off and the solvent was concentrated to give the title compound. MS
15 found: $(M + H)^+ = 584.5$.

Example 12

(±) N-((3S*)-1-[(1S*,2R*,4R*)-4-Isopropylamino-2-(4-methylsulfanyl-benzenesulfonylmethyl)-cyclohexyl]-3-methyl-2-oxo-pyrrolidin-3-yl)-3-trifluoromethyl-benzamide

20

(12a) Example 11 (16 mg) was dissolved in dichloroethane (1 mL) prior to the addition of glacial acetic acid (8 mg), acetone (8 mg), and NaBH(OAc)₃ (30 mg). After 20 h,
25 the solution was concentrated. The resulting residue was dissolved in EtOAc and washed with saturated NaHCO₃, water, and brine. The organic layer was dried, filtered, and concentrated. Reverse phase HPLC purification (gradient elution, water/acetonitrile/TFA) of the
30 resulting residue provided the title compound (13 mg).
MS found: $(M + H)^+ = 626.6$.

Example 13

(±) N-((3S*)-1-[(1S*,2R*,4R*)-4-(Isopropyl-methyl-amino)-2-(4-methylsulfanyl-benzenesulfonylmethyl)-cyclohexyl]-3-methyl-2-oxo-pyrrolidin-3-yl)-3-trifluoromethyl-benzamide

5

(13a) Example 12 (22 mg) was dissolved in MeOH (1 mL) prior to the addition of 37% formaldehyde in water (4 mg). After 15 min, NaBH₃CN (4 mg) was added. After 1 h, saturated NaHCO₃ was added and some of the MeOH was removed. EtOAc was added and the organic layer was dried, filtered, and concentrated. Reverse phase HPLC purification (gradient elution, water/acetonitrile/TFA) of the resulting residue provided the title compound (13 mg). MS found: (M + H)⁺ = 640.6.

15

Example 14

(±) N-((3S*)-1-[(1S*,2R*,4R*)-4-(Isopropyl-prop-2-ynyl-amino)-2-(4-methylsulfanyl-benzenesulfonylmethyl)-cyclohexyl]-3-methyl-2-oxo-pyrrolidin-3-yl)-3-trifluoromethyl-benzamide

20

(14a) Example 12 (20 mg) was dissolved in acetonitrile (1 mL) prior to the addition of K₂CO₃ (22 mg) and propargyl bromide (8 mg). After 4.75 h at 45 °C, the reaction was cooled to rt. Saturated NaHCO₃ was added and the reaction was extracted with EtOAc. The organic layer was dried, filtered, and concentrated. Reverse phase HPLC purification (gradient elution, water/acetonitrile/TFA) of the resulting residue provided the title compound (7 mg). MS found: (M + H)⁺ = 664.6.

30

Example 15

(±) N-((3S*)-1-[(1S*,2R*,4R*)-4-(Cyclopropylmethyl-
isopropyl-amino)-2-(4-methylsulfanyl-
benzenesulfonylmethyl)-cyclohexyl]-3-methyl-2-oxo-
pyrrolidin-3-yl)-3-trifluoromethyl-benzamide

(15a) Cyclopropanecarboxaldehyde was incorporated into Example 13 to give the title compound (11 mg). MS found: (M + H)⁺ = 680.6.

Example 16

N-((3S)-1-[4-(Isopropyl-methyl-amino)-2-(4-methylsulfanyl-benzenesulfonylmethyl)-cyclohexyl]-2-oxo-pyrrolidin-3-yl)-N-methyl-3-trifluoromethyl-benzamide

(16a) N(Me)Boc-L-Met-OH was incorporated into Example 10, step (10e), and advanced in an analogous way to Example 12. This procedure gave the title compound (31 mg) as a mixture of diastereomers. MS found: (M + H)⁺ = 640.3.

Example 17

N-((3S)-1-[(1S,2R,4R)-4-(Isopropyl-methyl-amino)-2-(4-methylsulfanyl-benzenesulfonylmethyl)-cyclohexyl]-2-oxo-pyrrolidin-3-yl)-3-trifluoromethyl-benzamide

(17a) N-Boc-L-Met-OH was incorporated into Example 16 to give the title compound. MS found: (M + H)⁺ = 626.3.

Example 18

1-((3S)-1-[(1S,2R,4R)-4-(Isopropyl-methyl-amino)-2-(4-methylsulfanyl-benzenesulfonylmethyl)-cyclohexyl]-2-oxo-pyrrolidin-3-yl)-3-(3-trifluoromethyl-phenyl)-urea

(18a) {(3S)-1-[(1S,2R,4R)-4-Azido-2-(4-methylsulfanyl-benzenesulfonylmethyl)-cyclohexyl]-2-oxo-pyrrolidin-3-yl}-carbamic acid tert-butyl ester (350 mg), from the synthesis of Example 17 (analogous to 10f), was dissolved in MeOH (5 mL) prior to the addition of 5% Pd/BaSO₄ (300 mg). A hydrogen balloon was added and the mixture was stirred. After stirring 1 h, the Pd/BaSO₄ was filtered off and the solvent was concentrated to give {(3S)-1-[(1S,2R,4R)-4-amino-2-(4-methylsulfanyl-benzenesulfonylmethyl)-cyclohexyl]-2-oxo-pyrrolidin-3-yl}-carbamic acid tert-butyl ester (497 mg). MS found: (M - H)⁻ = 496.5.

(18b) A portion of the above material (341 mg) was dissolved in dichloroethane (5 mL) prior to the addition of acetone (0.25 mL) and NaBH(OAc)₃ (436 mg). After 2 h, the solution was concentrated. The resulting residue was dissolved in EtOAc and washed with saturated NaHCO₃. The organic layer was dried, filtered, and concentrated. The resulting residue was dissolved in MeOH (2 mL) prior to the addition of 37% formaldehyde in water (0.1 mL). After 15 min, NaBH₃CN (111 mg) was added. After 2 h, saturated NaHCO₃ was added and some of the MeOH was removed. EtOAc was added and the organic layer was dried, filtered, and concentrated. This material was passed through a plug of silica and concentrated. This material (300 mg) was dissolved in CH₂Cl₂ (5 mL) prior to the addition of TFA (2.5 mL). After 30 min, it was concentrated and dried. A portion of the resulting residue (35 mg) was dissolved in DMF (1 mL) prior to the addition of 4-methylmorpholine (0.02 mL) and 3-trifluoromethylphenyl isocyanate (0.013 mL). After 2 h,

the solution was concentrated. Reverse phase HPLC purification (gradient elution, water/acetonitrile/TFA) of the resulting residue provided the title compound (7 mg). MS found: $(M + H)^+ = 641.3$.

5

Example 19

N-((3S)-1-[(1S,2R,4R)-4-(isopropyl-methyl-amino)-2-(4-methylsulfanyl-benzenesulfonylmethyl)-cyclohexyl]-2-oxo-pyrrolidin-3-yl)-3-trifluoromethyl-benzenesulfonamide

10

(19a) 3-(Trifluoromethyl)phenylsulfonyl chloride (instead of 3-trifluoromethylphenyl isocyanate) and pyridine (instead of 4-methylmorpholine) were incorporated into Example 18 to give the title compound. MS found: $(M + H)^+ = 662.3$.

15

Example 20

N-((3S)-1-[(1S,2R,4R)-4-(isopropyl-methyl-amino)-2-(4-methylsulfanyl-benzenesulfonylmethyl)-cyclohexyl]-2-oxo-pyrrolidin-3-yl)-benzamide

20

(20a) Benzoic acid was incorporated into Example 17 to give the title compound. MS found: $(M + H)^+ = 558.3$.

25

Example 21

((3S)-1-[(1S,2R,4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-2-oxo-pyrrolidin-3-yl)-3-(3-trifluoromethyl-phenyl)-urea

(21a) Example 18 (15 mg) was dissolved in MeOH (1 mL) prior to the addition of 20% Pd(OH)₂ (20 mg). A hydrogen balloon was added and the mixture was stirred. After stirring overnight, the palladium was filtered off and

the solvent was concentrated. Reverse phase HPLC purification (gradient elution, water/acetonitrile/TFA) of the resulting residue provided the title compound. MS found: $(M+H)^+ = 595.3$.

5

Example 22

N-[(3S)-1-((1S,2R,4R)-2-Benzenesulfonylmethyl-4-isopropylamino-cyclohexyl)-2-oxo-pyrrolidin-3-yl]-3-trifluoromethyl-benzamide

10

(22a) {(3S)-1-[(1S,2R,4R)-4-Azido-2-(4-methylsulfonyl-benzenesulfonylmethyl)-cyclohexyl]-2-oxo-pyrrolidin-3-yl}-carbamic acid tert-butyl ester (240 mg), see example 18, was dissolved in CH_2Cl_2 (5 mL) prior to the addition of TFA (2.5 mL). After 30 min, it was concentrated and dried. The resulting residue was dissolved in DMF prior to the addition of 4-methylmorpholine (0.25 mL) and 3-trifluoromethyl-benzoic acid (104.5 mg). BOP Reagent (64 mg) was added and the mixture was stirred for 40 min. After concentration, EtOAc was added along with 1N HCl solution. The EtOAc layer was washed with NaHCO_3 solution (aq) and brine, dried (MgSO_4), filtered, and concentrated. This material was passed through a plug of silica and concentrated. The resulting material (178 mg) was dissolved in MeOH (5 mL) prior to the addition of 20% $\text{Pd}(\text{OH})_2$ (100 mg). A hydrogen balloon was added and the mixture was stirred. After stirring overnight, the palladium was filtered off and the solvent was concentrated. A portion of this material (68 mg) was dissolved in dichloroethane (2.5 mL) prior to the addition of acetone (0.04 mL) and $\text{NaBH}(\text{OAc})_3$ (64 mg). After 40 min, the solution was concentrated. The

25
30

resulting residue was dissolved in EtOAc and washed with saturated NaHCO_3 . The organic layer was dried, filtered, and concentrated. Reverse phase HPLC purification (gradient elution, water/acetonitrile/TFA) of the
 5 resulting residue provided the title compound (66 mg).
 MS found: $(\text{M} + \text{H})^+ = 566.4$.

Example 23

N-((3S)-1-[(1S,2R,4R)-4-(Allyl-isopropyl-amino)-2-benzenesulfonylmethyl-cyclohexyl]-2-oxo-pyrrolidin-3-yl)-3-trifluoromethyl-benzamide

(23a) Example 22 (17 mg) was dissolved in DMF (1 mL) prior to the addition of K_2CO_3 (11 mg) and allyl bromide
 15 (0.003 mL). After stirring overnight, the reaction was filtered and concentrated. Reverse phase HPLC purification (gradient elution, water/acetonitrile/TFA) of the resulting residue provided the title compound (5 mg). MS found: $(\text{M} + \text{H})^+ = 606.3$.

20

Example 24

1-((1S,2R)-2-Benzenesulfonylmethyl-4-isopropylamino-cyclohexyl)-2-oxo-pyrrolidine-3-carboxylic acid (3-trifluoromethyl-phenyl)-amide

25

(24a) Phenyl disulfide was incorporated into Example 3, step 3d (in place of 4-bromophenyl disulfide), and advanced to step 3e to give (7R,8S)-(7-benzenesulfonylmethyl-1,4-dioxa-spiro[4.5]dec-8-yl)-
 30 carbamic acid benzyl ester. This material (1.2 g) was dissolved in MeOH prior to the addition of 10% Pd/C (250 mg). A hydrogen balloon was added and the mixture was stirred for 5 h. The Pd/C was filtered off and the

solvent was concentrated to give (7R, 8S)-7-benzenesulfonylmethyl-1,4-dioxaspiro[4.5]dec-8-ylamine (826 mg). MS found: $(M + H)^+ = 312.3$.

- 5 (24b) A portion of this material (239 mg) was dissolved in dichloroethane (4 mL) prior to the addition of 3,3-bis(methoxycarbonyl)propanal (160 mg) (Bunce et al. *Org. Prep. Proc. Int.* **1987**, 19, 67-71). The mixture was stirred for 1.5 h before $\text{NaBH}(\text{OAc})_3$ (195 mg) was added.
- 10 After 2 h, EtOAc and saturated NaHCO_3 was added. The organic layer was washed with additional saturated NaHCO_3 solution. The organic layer was dried, filtered, and concentrated to give (7R,8S)-2-[2-(7-benzenesulfonylmethyl-1,4-dioxaspiro[4.5]dec-8-ylamino)-ethyl]-malonic acid dimethyl ester (203 mg). MS found: $(M + H)^+ = 470.4$.
- 15

- (24c) A portion of this material (52 mg) was dissolved in MeOH prior to the addition of 0.5M NaOMe (0.05 mL) in
- 20 MeOH. The mixture was stirred overnight before being concentrated. EtOAc and 1N HCl was added. The organic layer was washed with additional 1N HCl solution. The organic layer was dried, filtered, and concentrated to give (1-(7-benzenesulfonylmethyl-1,4-dioxaspiro[4.5]dec-
- 25 8-yl)-2-oxo-pyrrolidine-3-carboxylic acid methyl ester (42 mg) as a mixture of diastereomers. MS found: $(M + H)^+ = 460.3$.

- (24d) A portion of this material (110 mg) was dissolved
- 30 in THF (1 mL), MeOH (0.5 mL), and water (0.5 mL) at 0 °C prior to the addition of 1M LiOH (0.25 mL) in water. The reaction was stirred for 2 h. EtOAc and 1N HCl was

added. The organic layer was washed with additional 1N HCl solution. The organic layer was dried, filtered, and concentrated to give 1-(7-benzenesulfonylmethyl-1,4-dioxo-spiro[4.5]dec-8-yl)-2-oxo-pyrrolidine-3-carboxylic acid (105 mg). MS found: $(M + H)^+ = 424.3$.

(24e) This material was dissolved in DMF prior to the addition of 4-methylmorpholine (0.08 mL) and 3-(trifluoromethyl)phenyl aniline (0.05 mL). HATU (114 mg) was added and the mixture was stirred overnight. EtOAc was added along with 1N HCl solution. The EtOAc layer was washed with NaHCO_3 solution and brine, dried (MgSO_4), filtered, and concentrated. Flash chromatography of the resulting residue gave 1-(7-benzenesulfonylmethyl-1,4-dioxo-spiro[4.5]dec-8-yl)-2-oxo-pyrrolidine-3-carboxylic acid (3-trifluoromethyl-phenyl)-amide. MS found: $(M + H)^+ = 567.3$.

(24f) A portion of this material (118 mg) was dissolved in acetone (1 mL) prior to the addition of 1N HCl (4 mL). The mixture was heated at reflux for 3 h. After cooling, the solution was concentrated. Flash chromatography of the resulting residue gave two diastereomers of 1-(2-benzenesulfonylmethyl-4-oxo-cyclohexyl)-2-oxo-pyrrolidine-3-carboxylic acid (3-trifluoromethyl-phenyl)-amide as top (MS found: $(M - H)^- = 521.3$) and bottom (MS found: $(M + \text{Na})^+ = 545.2$).

(24g) The above top diastereomer (53 mg) was dissolved in $\text{Ti}(\text{OiPr})_4$ (0.74 mL) prior to the addition of isopropylamine (0.08 mL). After 1.5 h, MeOH (1.5 mL) was added followed by NaBH_4 (11 mg). After 1 h, the reaction was quenched by the addition of 0.1N NaOH and filtered through celite. The filtrate was concentrated to a

mixture of diastereomers. Reverse phase HPLC purification (gradient elution, water/acetonitrile/TFA) of the resulting residue provided the title compound (15 mg) as a mixture of diastereomers. MS found: $(M + H)^+ = 566.3$.

5

Example 25

1-((1S,2R)-2-Benzenesulfonylmethyl-4-isopropylamino-cyclohexyl)-2-oxo-pyrrolidine-3-carboxylic acid (3-trifluoromethyl-phenyl)-amide

10

(25a) The above bottom diastereomer from 24f (71 mg) was dissolved in $Ti(OiPr)_4$ (0.7 mL) prior to the addition of isopropylamine (0.08 mL). After 1.5 h, MeOH (1.5 mL) was added followed by $NaBH_4$ (11 mg). After 1 h, the reaction was quenched by the addition of 0.1N NaOH and filtered through celite. The filtrate was concentrated to a mixture of diastereomers. Reverse phase HPLC purification (gradient elution, water/acetonitrile/TFA) of the resulting residue provided the title compound (22 mg) as a mixture of diastereomers. MS found: $(M + H)^+ = 566.5$.

20

Example 26

(2-((3S)-1-[(1S,2R)-2-(4-Methylsulfonyl-benzylamino)-cyclohexyl]-2-oxo-pyrrolidin-3-ylcarbamoyl)-4-trifluoromethyl-phenyl)-carbamic acid tert-butyl ester

25

(26a) Flash chromatography of the mixture of diastereomers in step (1c) gave the clean bottom isomer as {2-[(3S)-1-((1S,2R)-2-benzyloxycarbonylamino-cyclohexyl)-2-oxo-pyrrolidin-3-ylcarbamoyl]-4-trifluoromethyl-phenyl}-carbamic acid tert-butyl ester (MS found: $(M - H)^- = 617.2$).

30

(26b) A portion of this material (50 mg) was dissolved in MeOH (5 mL) prior to the addition of 10% Pd/C (10 mg). A hydrogen balloon was added and the mixture was stirred for 3 h. The Pd/C was filtered off and the solvent was concentrated. The resulting residue was dissolved in dichloroethane (1.4 mL) prior to the addition of glacial acetic acid (0.009 mL), 4-(methylthio)benzaldehyde (0.02 mL), and NaBH(OAc)₃ (31 mg). After 20 h, the solution was concentrated. The resulting residue was dissolved in EtOAc and washed with saturated NaHCO₃ solution. The organic layer was dried, filtered, and concentrated. Reverse phase HPLC purification (gradient elution, water/acetonitrile/TFA) of the resulting residue provided the title compound (15 mg). MS found: (M + H)⁺ = 621.4.

Example 27

N-{(3S)-1-[(1S,2R,4R)-2-Benzenesulfonylmethyl-4(R)-(isopropyl-propyl-amino)-cyclohexyl]-2-oxo-pyrrolidin-3-yl}-3-trifluoromethyl-benzamide

(27a) Propionaldehyde was incorporated into Example 5 (in the analogous step to 31) to give two diastereomers. The first diastereomer was the title compound (10 mg). MS found: (M + H)⁺ = 608.3.

Example 28

(±) 1-[(1S*,2R*,4R*)-4-Isopropylamino-2-(4-methylsulfanyl-benzenesulfonylmethyl)-cyclohexyl]-4-(3-trifluoromethyl-phenyl)-5,6-dihydro-1H-pyridin-2-one

(28a) Vinylmagnesium bromide (40 mL of a 1.0 M THF solution, 40 mmol) was added to a dry round bottom flask under nitrogen. The solution was cooled to -10 °C and

charged with *meta*-trifluoromethylbenzaldehyde (5.0 g, 29 mmol). The reaction was stirred for 1 h, warmed to RT and quenched with sat. NH_4Cl . The mixture was extracted with EtOAc three times, and the organic extracts were
5 dried (MgSO_4) and concentrated *in vacuo*. The crude material was purified via flash chromatography to give 1-(3-trifluoromethylphenyl)propen-1-ol as an oil (5.0 g, 87% yield). A portion of 1-(3-trifluoromethylphenyl)-propen-1-ol (0.5 g, 2.5 mmol) was dissolved in acetone
10 (20 mL). The resultant solution was cooled to 0 °C, treated with Jones reagent (1.14 mL of a 2.6 M solution, 2.96 mmol), and stirred for 10 minutes before being quenched with the addition of isopropyl alcohol (1.5 mL). The mixture was stirred for 5 min at rt, diluted with
15 Et_2O , filtered through Celite, washed with 10% Na_2SO_3 . The material was purified via filtration through a plug of silica gel (1:1 Et_2O :hexanes as eluant) to provide the 1-(3-trifluoromethylphenyl)propenone as an oil (320 mg, 65% yield), which solidified upon standing in the
20 freezer. ^1H -NMR (300 MHz, CDCl_3): δ 8.20 (s, 1H), 8.13 (d, 1H, J = 7.7 Hz), 7.84 (d, 1H, J = 9.0 Hz), 7.64 (t, 1H, J = 7.7 Hz), 7.16 (dd, 1H, J = 17.2, 10.6 Hz), 6.49 (dd, 1H, J = 17.2, 1.5 Hz), 6.03 (dd, 1H, J = 10.6, 1.5 Hz).

25 (28b) The compound (\pm) [(1S*,2R*,4R*)-4-azido-2-(4-methylsulfanyl-benzenesulfonylmethyl)-cyclohexyl]-carbamic acid tert-butyl ester (2.36 g, 5.36 mmol, see procedure 10d above) was dissolved in 2:1 CH_2Cl_2 /TFA and stirred at
30 rt for 1 h before being concentrated *in vacuo*. The resulting residue was redissolved in 1N NaOH and this solution was extracted twice with Et_2O . The extracts were combined, washed with brine, dried (MgSO_4),

filtered, and concentrated in vacuo. The product amine was dissolved in MeOH (40 mL), cooled to -10 °C, and treated with a solution of the 1-(3-trifluoromethylphenyl)propenone (1.09 g, 5.23 mmol) in MeOH (10 mL). The reaction was stirred for 30 min at rt, diluted with EtOAc, and washed successively with sat. NaHCO₃ and brine. The organic phase was dried (MgSO₄), filtered, and concentrated in vacuo. The resultant residue was purified by flash chromatography to give the desired (±) 3-[(1S*,2R*,4R*)-4-azido-2-(4-methylsulfonylmethyl)-benzenesulfonylmethyl)-cyclohexylamino]-1-(3-trifluoromethyl-phenyl)-propan-1-one (2.0 g, 69% yield). MS found: (M + H)⁺ = 541.3.

15 (28c) To a cooled (0 °C) solution of dimethylphosphonoacetic acid tert-butyl ester (0.44 mL, 2.22 mmol) in THF (20 mL) was added sodium hydride (94 mg, 60 wt% dispersion in oil, 2.35 mmol) in one portion. The mixture was stirred for 30 minutes at 0 °C and then charged with a solution of (±) 3-[(1S*,2R*,4R*)-4-azido-2-(4-methylsulfonylmethyl)-cyclohexylamino]-1-(3-trifluoromethyl-phenyl)-propan-1-one (0.75 g, 1.38 mmol) in THF. The reaction was stirred for 64 h at rt, quenched with sat. NH₄Cl, and extracted twice with EtOAc. The organic extracts were combined, washed with brine, dried (Na₂SO₄), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography to afford diastereomerically-pure (±) *E*-[5-[(1S*,2R*,4R*)-4-azido-2-(4-methylsulfonylmethyl)-benzenesulfonylmethyl)-cyclohexylamino]-3-(3-trifluoromethyl-phenyl)-pent-2-enoic acid tert-butyl ester] (0.26 g, 29% yield) and a number of impure

fractions of the same compound contaminated with its Z-diastereomer. MS found: $(M + H)^+ = 639.3$.

(28d) The compound (\pm) *E*-[5-[(1*S**,2*R**,4*R**)-4-azido-2-(4-methylsulfanyl-benzenesulfonylmethyl)-cyclohexylamino]-3-(3-trifluoromethyl-phenyl)-pent-2-enoic acid tert-butyl ester] (0.26 g, 0.4 mmol) was dissolved in 2:1 CH₂Cl₂/TFA and stirred at rt for 1 h before being concentrated in vacuo. The residue was redissolved in CH₂Cl₂ and concentrated in vacuo; this procedure was repeated once. The unpurified amino acid was dissolved in CH₂Cl₂, and the resulting solution was sequentially charged with *N,N*-diisopropylethylamine (0.3 mL, 1.6 mmol), 4-dimethylaminopyridine (54 mg, 0.44 mmol), and HATU (170 mg, 0.44 mmol). The mixture was stirred for 14 h at rt, quenched with sat. NH₄Cl, and extracted twice with EtOAc. The organic extracts were combined, washed with brine, dried (Na₂SO₄), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography to afford (\pm) 1-[(1*S**,2*R**,4*R**)-4-azido-2-(4-methylsulfanyl-benzenesulfonylmethyl)-cyclohexyl]-4-(3-trifluoromethyl-phenyl)-5,6-dihydro-1*H*-pyridin-2-one (0.2 g, 89% yield). The entirety of this material was dissolved in MeOH. The resultant solution was charged with 0.1 g of 10% Pd/BaSO₄, and the flask was evacuated and then back-filled with hydrogen (1 atm). This procedure was repeated several times. The reaction was stirred for 12 h and then filtered. The resultant solution was concentrated in vacuo to provide (\pm) 1-[(1*S**,2*R**,4*R**)-4-amino-2-(4-methylsulfanyl-benzenesulfonylmethyl)-cyclohexyl]-4-(3-trifluoromethyl-phenyl)-5,6-dihydro-1*H*-

pyridin-2-one (quantitative; ~90% purity). MS found: (M + H)⁺ = 538.

(28e) To a solution of (±) 1-[(1S*,2R*,4R*)-4-amino-2-(4-methylsulfanyl-benzenesulfonylmethyl)-cyclohexyl]-4-(3-trifluoromethyl-phenyl)-5,6-dihydro-1H-pyridin-2-one (0.36 mmol) in dichloroethane (6 mL) was added acetic acid (0.1 mL, 1.8 mmol), acetone (0.08 mL, 1.1 mmol), and sodium triacetoxyborohydride (0.23 g, 1.1 mmol). The mixture was heated at 80 °C for 1 h, cooled to rt, and quenched with sat. NaHCO₃, and extracted twice with EtOAc. The organic extracts were combined, washed with brine, dried (Na₂SO₄), filtered, and concentrated in vacuo. A portion of the crude residue was purified by reverse-phase HPLC to provide two fractions, one of which contained the title. MS found: (M + H)⁺ = 581.

Example 29

(±) 1-[(1S*,2R*,4R*)-4-Isopropylamino-2-(4-benzenesulfonylmethyl)-cyclohexyl]-4-(3-trifluoromethyl-phenyl)-5,6-dihydro-1H-pyridin-2-one

(29a) The title compound was isolated from a separate fraction of the reverse-phase HPLC purification described in procedure 28e above. MS found: (M + H)⁺ = 535.

Example 30

(±) 1-[(1S*,2R*,4R*)-4-Isopropylmethylamino-2-(4-methylsulfanyl-benzenesulfonylmethyl)-cyclohexyl]-4-(3-trifluoromethyl-phenyl)-5,6-dihydro-1H-pyridin-2-one

(30a) To a solution of (±) 1-[(1S*,2R*,4R*)-4-isopropylamino-2-(4-methylsulfanyl-benzenesulfonyl-

methyl)-cyclohexyl]-4-(3-trifluoromethyl-phenyl)-5,6-
 dihydro-1H-pyridin-2-one (0.18 mmol) in MeOH (4 mL) was
 added formaldehyde (0.09 mL of a 37 wt% solution in
 water, 1.08 mmol) and sodium cyanoborohydride (0.023 g,
 5 0.36 mmol). The reaction was stirred for 3 h, quenched
 with sat. NaHCO₃, and extracted twice with EtOAc. The
 organic extracts were combined, washed with brine, dried
 (Na₂SO₄), filtered, and concentrated in vacuo. The crude
 residue was purified by reverse-phase HPLC to provide the
 10 title compound. MS found: (M + H)⁺ = 595.4.

Example 31

15 (±) 1-[(1S*,2R*,4R*)-4-Amino-2-(4-methylsulfanyl-
 benzenesulfonylmethyl)-cyclohexyl]-4-(3-
 trifluoromethoxyphenyl)-5,6-dihydro-1H-pyridin-2-one

(31a) meta-Trifluoromethoxybenzaldehyde (4.63 g) was
 incorporated into procedure (28a) above to provide 1-(3-
 trifluoromethoxyphenyl)propenone (2.57 g, 50% yield). A
 20 portion of this material (0.35 g, 1.75 mmol) was carried
 through procedures (28b)-(28d) to give a residue, which
 was purified by reverse-phase HPLC to provide the title
 compound (0.043 g). MS found: (M + H)⁺ = 555.2.

25 Example 32

(±) 1-[(1S*,2R*,4R*)-4-Isopropylamino-2-(4-
 methylsulfanyl-benzenesulfonylmethyl)-cyclohexyl]-4-(3-
 trifluoromethoxyphenyl)-5,6-dihydro-1H-pyridin-2-one

30 (32a) The product of procedure (31a), (±) 1-
 [(1S*,2R*,4R*)-4-amino-2-(4-methylsulfanyl-benzene-
 sulfonylmethyl)-cyclohexyl]-4-(3-trifluoromethoxyphenyl)-
 5,6-dihydro-1H-pyridin-2-one (0.026 g, 0.046 mmol), was

carried through procedure (28e) above to afford the title compound (0.013 g, 47% yield) after purification by reverse-phase HPLC. MS found: $(M + H)^+ = 597.2$.

5

Example 33

(±) 1-[(1S*,2R*,4R*)-4-Isopropylamino-2-(4-benzenesulfonylmethyl)-cyclohexyl]-4-(3-trifluoromethyl-phenyl)-piperidin-2-one

10 (33a) The product of procedure (28e), (±) 1-[(1S*,2R*,4R*)-4-isopropylamino-2-(4-methylsulfonyl-benzenesulfonylmethyl)-cyclohexyl]-4-(3-trifluoromethyl-phenyl)-5,6-dihydro-1H-pyridin-2-one (~10 mg), was dissolved in MeOH. The resulting solution was charged
15 with ~20 mg 10% Pd/C, stirred under 1 atm of H₂ for 12 h, filtered, and concentrated in vacuo. The residue was redissolved in MeOH. The resulting solution was charged with ~40 mg 10% Pd/C, stirred under 55 atm of H₂ for 12 h, filtered, and concentrated in vacuo. The residue was
20 redissolved in MeOH. The resulting solution was charged with ~50 mg 10% Pd/C, stirred under 55 atm of H₂ for 36 h, filtered, and concentrated in vacuo. The residue was dissolved in 0.5% TFA/MeCN and concentrated in vacuo to afford a mixture of diastereomers as the title compound
25 as its TFA salt (10 mg). MS found: $(M + H)^+ = 537$.

Example 34

(S)-3-(3-(trifluoromethyl)benzylamino)-1-((1S,2R,4R)-4-(isopropyl(methyl)amino)-2-((4-(methylthio)phenylsulfonyl)methyl)cyclohexyl)pyrrolidin-2-one

(34a) 3-(Trifluoromethyl)benzaldehyde and sodium cyanoborohydride (instead of 3-trifluoromethylphenyl isocyanate) in MeOH (instead of DMF) were incorporated into Example 18 to give the title compound. MS found: (M + H)⁺ = 612.3.

Example 35

3(R)-(3-(trifluoromethyl)phenethyl)-1-((1S,2R,4R/S)-4-(isopropylamino)-2-(phenylsulfonylmethyl)cyclohexyl)pyrrolidin-2-one
trifluoroacetate

(35a) 3-(Trifluoromethyl)phenethyl alcohol (10.0 g, 52.6 mmol), triphenylphosphine (17.9 g, 68.4 mmol), and imidazole (5.00 g, 73.6 mmol) were dissolved in acetonitrile (42 mL) and ether (70 mL), then the mixture was cooled to 0 °C. Iodine (18.7 g, 73.6 mmol) was added in portions, then the mixture was stirred for 4 h. The reaction mixture was diluted with ether (1 L), washed with saturated Na₂S₂O₃ (3 x 300 mL), aqueous CuSO₄ (2 x 300 mL), and brine (2 x 300 mL), dried over Na₂SO₄, filtered, and concentrated to a volume of 200 mL. The precipitate of triphenylphosphineoxide was removed by filtration and the filtrate was triturated with ether/hexanes (2:1, 300 mL). Additional triphenylphosphine-oxide was removed by filtration, and the filtrate was concentrated to dryness to provide 1-(2-iodoethyl)-3-trifluoromethylbenzene as a yellow oil (16.5 g, quantitative): ¹H NMR (300 MHz, CDCl₃) δ 7.54–7.35 (m, 4H), 3.37 (t, J = 8.3 Hz, 2H), 3.24 (t, J = 8.3 Hz, 2H); ¹⁹F NMR (282 MHz, CDCl₃) δ -63.1.

(35b) To a 100-mL three-neck round-bottomed flask equipped with a thermometer, addition funnel, and nitrogen inlet was added diisopropylamine (2.4 mL, 17.2 mmol) in THF (4 mL). The solution was cooled to -78 °C, then a solution of *n*-BuLi (2.5 M in hexanes, 6.9 mL) was added slowly, followed by HMPA (3.1 mL, 18.0 mmol) and the reaction was stirred at this temperature for 30 min. A solution of ethylpent-4-enoate (2.0 g, 15.6 mmol) in THF (15.6 mL) was added dropwise, then the mixture was stirred for 45 min. To this mixture was added a solution of 1-(2-iodoethyl)-3-trifluoromethylbenzene (35a) (1.37 g, 4.58 mmol) in THF (2 mL) and the resulting mixture was allowed to warm to room temperature overnight. The mixture was diluted with ether (500 mL), washed with water (2 x 250 mL), and brine (2 x 250 mL), dried over Na₂SO₄, filtered, and evaporated. The residue was purified by flash chromatography to provide 2-[2-(3-trifluoromethylphenyl)ethyl]pent-4-enoic acid ethyl ester (529 mg, 39%) as a colorless oil: ESI MS *m/z* 301 [C₁₆H₁₉F₃O₂ + H]⁺.

(35c) 2-[2-(3-Trifluoromethylphenyl)ethyl]pent-4-enoic acid ethyl ester (529 mg, 1.76 mmol) was dissolved in CH₂Cl₂ and cooled to -78 °C. The resulting solution was treated with ozone until a light blue color was observed. The solution was degassed with N₂, then polymer-supported Ph₃P (3 mmol/g, 882 mg, 2.64 mmol) was added and the mixture was stirred for 3 h at room temperature. The solid was removed by filtration and rinsed with CH₂Cl₂. Evaporation of the filtrate provided an oil, which was purified by flash column chromatography (hexanes/ether) to give ethyl 2-((1,2,3-trioxolan-4-yl)methyl)-4-(3-(trifluoromethyl)phenyl)butanoate as a colorless oil (151

mg, 25%) and the desired ethyl 2-(2-oxoethyl)-4-(3-(trifluoromethyl)phenyl)butanoate as a colorless oil (83 mg, 16%). A solution of ethyl 2-((1,2,3-trioxolan-4-yl)methyl)-4-(3-(trifluoromethyl)phenyl)butanoate (150
 5 mg, 431 μmol) in CH_2Cl_2 (20 mL) was cooled to $-78\text{ }^\circ\text{C}$, then Me_2S (0.3 mL, 4.1 mmol) was added and the mixture was stirred for 2 d. The reaction mixture was diluted with CH_2Cl_2 (300 mL), washed with water (2 x 100 mL), and brine (100 mL), dried over Na_2SO_4 , filtered, and evaporated to
 10 provide additional ethyl 2-(2-oxoethyl)-4-(3-(trifluoromethyl)phenyl)butanoate (123 mg): ^1H NMR (300 MHz CDCl_3) δ 7.50–7.30 (m, 4H), 5.26–5.20 (m, 1H), 5.14 (d, J = 1.6 Hz, 1H), 5.04 (d, J = 6.3 Hz, 1H), 4.37 (q, J = 7.0 Hz, 2H), 2.73–2.57 (m, 3H), 2.35–1.77 (m, 4H), 1.29
 15 (t, J = 7.1 Hz, 3H); ^{19}F NMR (282 MHz, CDCl_3) δ -63.0.

(35d) Ethyl 2-(2-oxoethyl)-4-(3-(trifluoromethyl)phenyl)butanoate (83 mg, 275 μmol) and (7R, 8S)-7-(benzene-4-sulfonylmethyl)-1,4-dioxaspiro[4.5]dec-8-ylamine [3g by substitution of phenyl
 20 disulfide into step (3d) and skipping step (3f)] (68 mg, 218 μmol) were dissolved in 1,2-dichloroethane (2.3 mL). The resulting solution was stirred at room temperature for 10 min, then sodium triacetoxyborohydride (58 mg, 275
 25 μmol) was added and the mixture was stirred overnight. The reaction mixture was diluted with CH_2Cl_2 (400 mL), washed with saturated NH_4Cl (3 x 150 mL), and brine (200 mL), dried over Na_2SO_4 , filtered and evaporated. The residue was purified by flash column chromatography to
 30 give an inseparable mixture of diastereomers 4-(7-benzenesulfonylmethyl-1,4-dioxaspiro[4.5]dec-8-ylamino)-

2-[2-(3-trifluoromethylphenyl)ethyl]butyric acid ethyl ester (64 mg, 49%): ESI MS m/z 598 [$C_{30}H_{38}F_3NO_6S + H$]⁺.

(35e) The mixture of diastereomers from above (35d) (92 mg, 154 mmol) was dissolved in MeOH (10 mL) and NaOMe (85 mg) was added. The mixture was heated at 50 °C for 16 h, then diluted with EtOAc (300 mL). The mixture was washed with water (3 x 150 mL) and brine (200 mL), dried over Na₂SO₄, and evaporated in vacuo to dryness. The residue was purified by flash column chromatography to provide (1S, 2R)-1-(7-benzenesulfonylmethyl-1,4-dioxaspiro[4.5]dec-8-yl)-3(R)-[2-(3-trifluoromethylphenyl)ethyl]pyrrolidin-2-one (upper TLC spot; 30 mg, 35%): ¹H NMR (300 MHz, CDCl₃) δ 7.88–7.80 (m, 2H), 7.62–7.35 (m, 7H), 4.03–3.70 (m, 6H), 3.52–3.39 (m, 1H), 3.37–3.25 (m, 1H), 3.06 (dd, J = 14.6, 2.1 Hz, 1H), 2.88–2.67 (m, 3H), 2.33–1.55 (m, 11H); ¹⁹F NMR (282 MHz, CDCl₃) δ -63.0; ESI MS m/z 552 [$C_{28}H_{32}F_3NO_5S + H$]⁺; and (1S, 2R)-1-(7-benzenesulfonylmethyl-1,4-dioxaspiro[4.5]dec-8-yl)-3(S)-[2-(3-trifluoromethylphenyl)ethyl]pyrrolidin-2-one (lower TLC spot; 34 mg, 41%) ¹H NMR (300 MHz, CDCl₃) δ 7.88–7.80 (m, 2H), 7.60–7.35 (m, 7H), 4.03–3.73 (m, 6H), 3.40–3.25 (m, 2H), 2.97 (dd, J = 14.3, 1.9 Hz, 1H), 2.80–2.62 (m, 3H), 2.40–1.40 (m, 11H); ¹⁹F NMR (282 MHz, CDCl₃) δ -63.0; ESI MS m/z 552 [$C_{28}H_{32}F_3NO_5S + H$]⁺.

(35f) (1S, 2R)-1-(7-benzenesulfonylmethyl-1,4-dioxaspiro[4.5]dec-8-yl)-3(R)-[2-(3-trifluoromethylphenyl)ethyl]pyrrolidin-2-one (29 mg, 53 mmol) and *p*-TsOH (4 mg) in acetone (5 mL) was stirred overnight at room temperature. A second portion of *p*-TsOH (4 mg) was added and the reaction mixture was stirred for an additional 24 h. The solvent was

evaporated in vacuo and the residue was purified by flash column chromatography to afford (R)-3-(3-(trifluoromethyl)phenethyl)-1-((1S,2R)-4-oxo-2-(phenylsulfonylmethyl)cyclohexyl)pyrrolidin-2-one (17 mg, 5 64%) as a white solid: ESI MS m/z 508 $[\text{C}_{26}\text{H}_{28}\text{F}_3\text{NO}_4\text{S} + \text{H}]^+$.

(35g) To a stirred mixture of the above compound (35f) (17 mg, 34 mmol) and titanium(IV) isopropoxide (0.5 mL, 1.67 mmol) was added 2-propylamine (36 mg, 600 mmol). 10 The mixture was stirred at room temperature for 3 h, then MeOH (5 mL) was added, followed by NaBH_4 (3.5 mg, 94 mmol). After 2 h, the reaction mixture was quenched with 0.5 M NaOH (30 mL) and the resulting mixture was stirred for 2 h. The mixture was diluted with EtOAc (400 mL), 15 washed with 0.5 M NaOH (3 x 150 mL) and brine (200 mL), dried over Na_2SO_4 , filtered, and evaporated. Purification of the residue by semi-preparative HPLC gave the title compound (10 mg) as a mixture of diastereomers: ^1H NMR (300 MHz, CDCl_3) δ 8.00–7.75 (m, 2H), 7.73–7.30 (m, 7H), 20 4.60–1.50 (m, 20H), 1.49–1.20 (m, 6H).

Example 36

3(S)-(3-(Trifluoromethyl)phenethyl)-1-((1S,2R,4R/S)-4-
(isopropylamino)-2-
 25 (phenylsulfonylmethyl)cyclohexyl)pyrrolidin-2-one
trifluoroacetate

(36a) (1S, 2R)-1-(7-Benzenesulfonylmethyl-1,4-dioxaspiro[4.5]dec-8-yl)-3(S)-[2-(3- 30 trifluoromethylphenyl)ethyl]pyrrolidin-2-one (see, 35e) was incorporated into Example 35, step (35f) to give the

title compound as a mixture of diastereomers. MS found:
 $(M + H)^+ = 551.4$.

Example 37

5 N-((S)-1-((1S,2R,4R)-4-(isopropyl(methyl)amino)-2-
 (phenylsulfonylmethyl)cyclohexyl)-2-oxoazepan-3-yl)-3-
 (trifluoromethyl)benzamide trifluoroacetate

(37a) To a solution of (S)-2-tert-butoxycarbonylamino-6-
 10 hydroxy-hexanoic acid (1 g, 6 mmol) in 30 mL of CH_2Cl_2 and
 5 mL of MeOH at rt was slowly added $TMSCHN_2$ (10 mL), and
 the reaction mixture was left with stirring for 1 h. The
 solvent was remove under reduced pressure, and the
 resulting residue was diluted with water and EtOAc. The
 15 organic layer was separated, dried over Na_2SO_4 , and
 concentrated to afford an oil (S)-2-tert-
 butoxycarbonylamino-6-hydroxy-hexanoic acid methyl ester.
 MS $[M + H]^+ 262$.

20 (37b) To a solution of oxalyl chloride (0.33 mL, 0.36
 mmol) in CH_2Cl_2 (10 mL) at $-78^\circ C$ was added DMSO (0.1 mL,
 1.32 mmol). Ten minutes later, a solution of alcohol
 (S)-2-tert-butoxycarbonylamino-6-hydroxy-hexanoic acid
 methyl ester (144 mg, 0.55 mmol) in CH_2Cl_2 (10 mL) was
 25 added and stirred for 15 min before iPr_2NEt (0.5 mL, 2.7
 mmol) was added. The reaction mixture was allowed to
 warm up to $0^\circ C$ and left with stirring for 2 h before
 water and EtOAc were added. The organic layer was
 separated, dried over Na_2SO_4 , and concentrated to afford
 30 to a crude oil (S)-2-tert-butoxycarbonylamino-6-oxo-
 hexanoic acid methyl ester.

(37c) To a solution of (1S*,2R*,4R*)-4-azido-2-
 benzenesulfonylmethyl-cyclohexylamine (see example 10,

steps 10a-10d with the substitution of methyl phenyl sulfone in step 10a and then treated with TFA) (135 mg, 0.45 mmol) and (S)-2-tert-butoxycarbonylamino-6-oxo-hexanoic acid methyl ester (140 mg, 0.55 mmol) in CH_2Cl_2 (15 mL) at rt was added $\text{NaBH}(\text{OAc})_3$ (194 mg, 0.9 mmol). After 16 h, the solution was concentrated. The resulting residue was re-dissolved in EtOAc and washed with saturated NaHCO_3 , water, and brine. The organic layer was dried, filtered, and concentrated to afford to a crude oil (1S,2R,3S,4R)-6-(4-azido-2-benzenesulfonylmethyl-cyclohexylamino)-2-tert-butoxycarbonylamino-hexanoic acid methyl ester. MS $[\text{M} + \text{H}]^+ = 538$.

(37d) To a solution of (1S,2R,3S,4R)-6-(4-azido-2-benzenesulfonylmethyl-cyclohexylamino)-2-tert-butoxycarbonylamino-hexanoic acid methyl ester (270 mg) in THF (15 mL) and H_2O (3 mL) at rt was added LiOH (24 mg). After 1 h, the reaction was diluted with water and EtOAc. Upon adjusting the pH value to 7, the organic layer was collected, dried, and concentrated to afford to a crude oil (140 mg) which was re-dissolved in DMF (15 mL), followed by the addition of HATU (132 mg, 0.34 mmol) and Hunig's base (0.06 mL, 0.34 mmol). The resulting mixture was stirred for 16 before EtOAc was added. The EtOAc layer was washed with 1 N HCl, NaHCO_3 solution (aq), and brine. The EtOAc was dried (MgSO_4), filtered, and concentrated. Flash chromatography of the resulting residue gave [(3S)-1-(1S,2R,4R)-(4-azido-2-benzenesulfonylmethyl-cyclohexyl)-2-oxo-azepan-3-yl]-carbamic acid tert-butyl ester (120 mg). MS found: $(\text{M} + \text{H})^+ = 506$.

(37e) To a solution of [(3S)-1-(1S,2R,4R)-(4-azido-2-benzenesulfonylmethyl-cyclohexyl)-2-oxo-azepan-3-yl]-carbamic acid tert-butyl ester (120 mg) in CH_2Cl_2 (10 mL) was added TFA (3.3 mL). After 45 min, the solution was diluted with NaHCO_3 solution (aq) and EtOAc. The organic

layer was collected, dried, and concentrated to afford to a crude oil 3-amino-(3S)-1-(1S,2R,4R)-(4-azido-2-benzenesulfonylmethyl-cyclohexyl)-azepan-2-one. MS $[M + H]^+ = 406$.

5

(37f) To a solution of 3-amino-(3S)-1-(1S,2R,4R)-(4-azido-2-benzenesulfonylmethyl-cyclohexyl)-azepan-2-one (50 mg, 0.12 mmol) in DMF (15 mL) was added 3-trifluoromethyl benzoic acid (28 mg, 0.15 mmol), HATU (57 mg, 0.15 mmol) and Hunig's base (0.03 mL, 0.15 mmol). The resulting mixture was stirred for 16 h before EtOAc was added. The EtOAc layer was washed with 1 N HCl, NaHCO₃ solution (aq), and brine. The EtOAc was dried (MgSO₄), filtered, and concentrated. Flash chromatography of the resulting residue gave N-[(3S)-1-(1S,2R,4R)-(4-azido-2-benzenesulfonylmethyl-cyclohexyl)-2-oxo-azepan-3-yl]-3-trifluoromethyl-benzamide (70 mg). MS found: $(M + H)^+ = 578$.

(37g) N-[(3S)-1-(1S,2R,4R)-(4-Azido-2-benzenesulfonylmethyl-cyclohexyl)-2-oxo-azepan-3-yl]-3-trifluoromethyl-benzamide (70 mg) was dissolved in MeOH (10 mL) prior to the addition of 10% Pd/C (20 mg). A hydrogen balloon was added and the solution was stirred at rt for 16 h. The palladium was filtered and the solvent was concentrated to N-[(3S)-1-(1S,2R,4R)-(4-amino-2-benzenesulfonylmethyl-cyclohexyl)-2-oxo-azepan-3-yl]-3-trifluoromethyl-benzamide. MS found: $(M + H)^+ = 552$.

30

(37h) To a solution of N-[(3S)-1-(1S,2R,4R)-(4-amino-2-benzenesulfonylmethyl-cyclohexyl)-2-oxo-azepan-3-yl]-3-trifluoromethyl-benzamide (30 mg) in CH₂Cl₂ (15 mL) at rt was added NaBH(OAc)₃ (50 mg), acetone (2 mL), and three drops of AcOH. After 2 h, formaldehyde (2 mL) was added and the solution was stirred for another 2 h. The reaction mixture was diluted with EtOAc and washed with

saturated NaHCO₃, water, and brine. The organic layer was dried, filtered, and concentrated to afford to a crude oil which was purified by semi-preparative HPLC to give the title compound. MS [M + H]⁺ = 608.

5

Example 38

N-((S)-1-((1S,2R,4R)-4-(dimethylamino)-2-(phenylsulfonylmethyl)cyclohexyl)-2-oxopiperidin-3-yl)-3-(trifluoromethyl)benzamide trifluoroacetate

10

(38a) (S)-2-tert-Butoxycarbonylamino-5-hydroxy-pentanoic acid benzyl ester was incorporated into Example 37 (without acetone in step 37h) to give the title compound. MS found: (M + H)⁺ = 566.

15

Example 39

(R*)-1-((1S*,2R*,4R*)-4-(isopropyl(methyl)amino)-2-(phenylsulfonylmethyl)cyclohexyl)-3-((2-(3-(trifluoromethyl)phenyl)-1,3-dioxolan-2-yl)methyl)pyrrolidin-2-one

20

(39a) A mixture of methyl 3-bromopropionate (**6a**, 10.0 g, 60.0 mmol) and sodium iodide (11.2 g, 74.9 mmol) in acetone (60 mL) was stirred for 30 min at room

25

temperature, then heated at reflux for 40 min. The mixture was cooled in an ice/water bath and the white solid was filtered off, rinsing with acetone. The

filtrate was evaporated to dryness to provide methyl 3-iodopropionate (12.3 g, 96%) as a yellow oil: ¹H NMR (300

30

MHz, CDCl₃) δ 3.73 (s, 3H), 3.33 (t, J = 7.2 Hz, 2H), 2.99 (t, J = 7.2 Hz, 2H).

(39b) To a 250-mL three-neck round-bottomed flask equipped with a thermometer, condenser, and nitrogen inlet was added Zn-Cu couple (3.41 g, 52.1 mmol). A solution of methyl 3-iodopropionate (7.27 g, 34.0 mmol) in benzene (67.7 mL) and DMA (4.5 mL) was added over 5 min and the mixture was stirred at room temperature for 1 h, then heated at 60 °C for 5 h. A mixture of Pd(PPh₃)₄ (1.05 g, 0.906 mmol) in benzene (22.7 mL) was added to the reaction and stirred at 60 °C for 5 min. The mixture was then removed from heat and 3-(trifluoromethyl)benzoyl chloride (3.4 mL, 23 mmol) in benzene (11.3 mL) was added immediately. After stirring for 2 h, the mixture was diluted with EtOAc, washed with 1 M HCl (3 × 200 mL), NaHCO₃ (2 × 200 mL) and brine (1 × 200 mL), dried over Na₂SO₄, filtered, and evaporated. The crude material was purified by CombiFlash chromatography (silica, 0-70% ether/hexanes) to give 4-oxo-4-(3-trifluoromethylphenyl)butyric acid methyl ester (5.35 g, 91%) as an orange oil: ¹H NMR (300 MHz CDCl₃) δ 8.24 (s, 1H), 8.17 (d, *J* = 7.8 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 3.72 (s, 3H), 3.35 (t, *J* = 6.5 Hz, 2H), 2.81 (t, *J* = 6.5 Hz, 2H); ¹⁹F NMR (282 MHz, CDCl₃) δ -63.3; ESI MS *m/z* 261 [C₁₂H₁₁F₃O₃ + H]⁺.

(39c) A solution of 4-oxo-4-(3-trifluoromethylphenyl)butyric acid methyl ester (2.47 g, 9.50 mmol), trimethylorthoformate (4.8 mL), *p*-TsOH (181 mg, 0.95 mmol) and ethylene glycol (7.3 mL) was heated at 50 °C for 3 h. The mixture was diluted with EtOAc (500 mL), washed with saturated NaHCO₃ (3 × 200 mL), water (2 × 200 mL), and brine (150 mL), dried over Na₂SO₄, filtered and evaporated to give a mixture of esters. The mixture was stirred in MeOH (25 mL) with NaOMe (400 mg) at room

temperature for 6 h. The reaction was quenched with saturated NH_4Cl and the methanol was removed by evaporation. The residue was dissolved in EtOAc, washed with saturated NH_4Cl (2 \times 200 mL), water (2 \times 200 mL) and
 5 brine (200 mL), dried over Na_2SO_4 , and evaporated to give 3-[2-(3-trifluoromethylphenyl)-[1,3]dioxolan-2-yl]propionic acid methyl ester (2.71 g, 94%) as a light yellow oil: ^1H NMR (300 MHz, CDCl_3) δ 7.73 (s, 1H), 7.65 (d, J = 7.7 Hz, 1H), 7.56 (d, J = 7.7 Hz, 1H), 7.47 (t, J = 7.7 Hz, 1H), 4.10–3.99 (m, 2H), 3.80–3.70 (m, 2H), 3.65 (s, 3H), 2.44 (t, J = 7.8 Hz, 2H), 2.24 (t, J = 7.8 Hz, 2H); ^{19}F NMR (282 MHz, CDCl_3) δ -62.9; ESI MS m/z 305 [$\text{C}_{14}\text{H}_{15}\text{F}_3\text{O}_4$ + H] $^+$.

15 (39d) Diisopropylamine (1.74 mL, 12.5 mmol) was dissolved in THF (6.2 mL) under a nitrogen atmosphere and cooled to -78 $^\circ\text{C}$. A solution of n -BuLi (2.5 M in hexanes, 5.3 mL) was added dropwise, keeping the temperature below -67 $^\circ\text{C}$. The reaction was warmed to -15 $^\circ\text{C}$ for 15 min, then cooled
 20 back down to -78 $^\circ\text{C}$. A solution of 3-[2-(3-trifluoromethylphenyl)-[1,3]dioxolan-2-yl]propionic acid methyl ester (2.71 g, 8.90 mmol) in THF (1.5 mL) was added and the mixture was stirred for 40 min. Allyl bromide (0.92 mL, 11 mmol) and HMPA (0.46 mL, 2.7 mmol)
 25 were added simultaneously and the reaction was stirred at room temperature overnight. The mixture was diluted with EtOAc (400 mL), washed with saturated NH_4Cl (3 \times 150 mL), water (2 \times 150 mL), and brine (200 mL), dried over Na_2SO_4 , filtered, and evaporated. The residue was
 30 purified by CombiFlash chromatography (silica, 0–40% ether/heptane) to give 2-[2-(3-trifluoromethylphenyl)-[1,3]dioxolan-2-ylmethyl]pent-4-enoic acid methyl ester (1.82 g, 59%) as a light yellow oil: ^1H NMR (300 MHz,

CDCl₃) δ 7.73 (s, 1H), 7.64 (d, J = 7.7 Hz, 1H), 7.56 (d, J = 7.7 Hz, 1H), 7.46 (t, J = 7.7 Hz, 1H), 5.80–5.61 (m, 1H), 5.10–4.97 (m, 2H), 4.10–3.90 (m, 2H), 3.80–3.60 (m, 5H), 2.83–2.68 (m, 1H), 2.50–2.13 (m, 3H), 1.97 (dd, J = 14.7, 2.7 Hz, 1H); ¹⁹F NMR (282 MHz, CDCl₃) δ -62.9; ESI MS m/z 345 [C₁₇H₁₉F₃O₄ + H]⁺.

(39e) A solution of 2-[2-(3-trifluoromethylphenyl)-[1,3]dioxolan-2-ylmethyl]pent-4-enoic acid methyl ester (1.82 g, 5.29 mmol) in CH₂Cl₂ (250 mL) was cooled to -78 °C and ozone was bubbled into the solution until a light blue solution was obtained. The solution was degassed with nitrogen, then dimethylsulfide (4 mL) was added dropwise. The mixture was stirred overnight at room temperature, then heated at reflux for 24 h. The reaction was diluted with CH₂Cl₂ (500 mL), washed with 1 M HCl (3 × 150 mL) and brine (200 mL), dried over Na₂SO₄, filtered, and evaporated. The residue was purified by CombiFlash chromatography (silica, 0–50% ether/hexanes) to give aldehyde 4-oxo-2-[2-(3-trifluoromethylphenyl)-[1,3]dioxolan-2-ylmethyl]butyric acid methyl ester (1.41 g, 77%) as a yellow oil: ¹H NMR (300 MHz, CDCl₃) δ 9.74 (s, 1H), 7.72 (s, 1H), 7.63 (d, J = 7.7 Hz, 1H), 7.57 (d, J = 7.7 Hz, 1H), 7.47 (t, J = 7.7 Hz, 1H), 4.12–3.95 (m, 2H), 3.83–3.64 (m, 5H), 3.27–3.13 (m, 1H), 2.98–2.70 (m, 2H), 2.40 (dd, J = 14.8, 7.2 Hz, 1H), 2.04 (dd, J = 14.8, 5.5 Hz, 1H); ¹⁹F NMR (282 MHz, CDCl₃) δ -62.9.

(39f) A mixture of (1S*,2R*,4R*)-4-azido-2-benzenesulfonylmethyl-cyclohexylamine (see 37c) (676 mg, 2.30 mmol) and 4-oxo-2-[2-(3-trifluoromethylphenyl)-[1,3]dioxolan-2-ylmethyl]butyric acid methyl ester (794

mg, 2.30 mmol) in 1,2-dichloroethane (46 mL) was stirred at room temperature overnight. The solvent was removed under vacuum, then the residue was dissolved in MeOH (35 mL) and cooled to 0 °C. Sodium borohydride (872 mg, 23.0 mmol) was added in one portion and the mixture was stirred for 4 h. The reaction was diluted with EtOAc (500 mL), washed with saturated NaHCO₃ (3 × 150 mL) and brine (200 mL), dried over Na₂SO₄, filtered, and evaporated. The residue was purified by CombiFlash chromatography (silica, 0-100% ether/hexanes) to give a mixture of diastereomers methyl 4-((1S*,2R*,4R*)-4-azido-2-(phenylsulfonylmethyl)cyclohexylamino)-2-((2-(3-(trifluoromethyl)phenyl)-1,3-dioxolan-2-yl)methyl)butanoate (1.04 g, 70%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 8.00-7.88 (m, 2H), 7.75-7.52 (m, 6H), 7.51-7.41 (m, 1H), 4.17-3.88 (m, 2H), 3.80-3.60 (m, 5H), 3.59-3.48 (m, 1H), 3.45-3.30 (m, 1H), 3.10-2.98 (m, 1H), 2.85-2.55 (m, 3H), 2.50-2.20 (m, 3H), 2.00-1.30 (m, 9H); ¹⁹F NMR (282 MHz, CDCl₃) δ -62.9, -62.8; ESI MS m/z 625 [C₂₉H₃₅F₃N₄O₆S + H]⁺.

(39g) A stirred mixture of diastereomers 39f (1.04 g, 1.66 mmol) and NaOMe (90 mg, 1.66 mmol) in MeOH (20 mL) was heated at reflux for 4 d. The solvent was removed under vacuum and the residue was dissolved in EtOAc (350 mL). The organic mixture was washed with saturated NH₄Cl (3 × 100 mL), water (200 mL), and brine (200 mL), dried over Na₂SO₄, filtered, and evaporated. The crude material was purified by CombiFlash chromatography followed by preparative TLC to give (S*)-1-((1S*,2R*,4R*)-4-azido-2-(phenylsulfonylmethyl)cyclohexyl)-3-((2-(3-(trifluoromethyl)phenyl)-1,3-dioxolan-2-yl)methyl)pyrrolidin-2-one (39g-a, 359 mg, 36%) and (R*)-

1-((1S*,2R*,4R*)-4-azido-2-(phenylsulfonylmethyl)cyclohexyl)-3-((2-(3-(trifluoromethyl)phenyl)-1,3-dioxolan-2-yl)methyl)pyrrolidin-2-one (39g-b, 322 mg, 33%) as white solids.

For 39g-a: ^1H NMR (300 MHz, CDCl_3) δ 7.90–7.82 (m, 2H), 7.73 (s, 1H), 7.70–7.43 (m, 6H), 4.10–3.90 (m, 3H), 3.81–3.57 (m, 3H), 3.55–3.42 (m, 1H), 3.40–3.20 (m, 3H), 2.61–2.47 (m, 3H), 2.27–2.10 (m, 2H), 2.00–1.63 (m, 7H); ^{19}F NMR (282 MHz, CDCl_3) δ -62.9; ESI MS m/z 593 [$\text{C}_{28}\text{H}_{31}\text{F}_3\text{N}_4\text{O}_5 + \text{H}$] $^+$.

For 39g-b: ^1H NMR (300 MHz, CDCl_3) δ 7.90–7.82 (m, 2H), 7.73 (s, 1H), 7.69–7.43 (m, 6H), 4.10–3.90 (m, 3H), 3.85–3.57 (m, 3H), 3.44–3.23 (m, 3H), 3.22–3.10 (m, 1H), 2.62–1.60 (m, 12H); ^{19}F NMR (282 MHz, CDCl_3) δ -62.9; ESI MS m/z 593 [$\text{C}_{28}\text{H}_{31}\text{F}_3\text{N}_4\text{O}_5\text{S} + \text{H}$] $^+$.

(39h) A mixture of 39g-b (222 mg, 375 μmol) and 10% Pd/C (239 mg, 112 μmol) in MeOH (150 mL) was hydrogenated (50 psi) for 2 h. The mixture was filtered through diatomaceous earth (infusorial earth) and the filtrate was evaporated under vacuum to give (R*)-1-((1S*,2R*,4R*)-4-amino-2-(phenylsulfonylmethyl)cyclohexyl)-3-((2-(3-(trifluoromethyl)phenyl)-1,3-dioxolan-2-yl)methyl)pyrrolidin-2-one (39h-b, 169 mg, 80%) as a white solid: ^1H NMR (300 MHz, CDCl_3) δ 7.87 (d, $J = 7.3$ Hz, 2H), 7.68–7.35 (m, 7H), 4.22 (s, 1H), 4.02–3.60 (m, 5H), 3.50–3.14 (m, 4H), 2.80–2.63 (m, 1H), 2.60–1.60 (m,

12H); ^{19}F NMR (282 MHz, CDCl_3) δ -62.8; ESI MS m/z 567 [$\text{C}_{28}\text{H}_{33}\text{F}_3\text{N}_2\text{O}_5\text{S} + \text{H}$] $^+$.

(39i) A mixture of 39h-b (170 mg, 300 μmol), acetone (871 μL , 11.9 μmol), acetic acid (69.1 μL , 1.20 mmol), and sodium triacetoxymethylborohydride (255 mg, 1.20 mmol) in dichloroethane (17 mL) was stirred at room temperature for 2 h. The reaction was diluted with EtOAc (500 mL), washed with saturated NaHCO_3 (3 \times 150 mL), water (2 \times 100 mL), and brine (150 mL), dried over Na_2SO_4 , filtered, and evaporated. The residue was purified by CombiFlash chromatography (silica, 0-10% $\text{MeOH}/\text{CH}_2\text{Cl}_2$) to provide (R*)-1-((1S*,2R*,4R*)-4-(isopropylamino)-2-(phenylsulfonylmethyl)cyclohexyl)-3-((2-(3-(trifluoromethyl)phenyl)-1,3-dioxolan-2-yl)methyl)pyrrolidin-2-one (39i-b, 106 mg, 58%) as a white solid: ^1H NMR (300 MHz, CDCl_3) δ 7.89 (d, J = 7.2 Hz, 2H), 7.68 (s, 1H), 7.64-7.39 (m, 6H), 4.20 (s, 1H), 4.05-3.90 (m, 2H), 3.81-3.60 (m, 3H), 3.48-3.11 (m, 4H), 3.10-2.88 (m, 1H), 2.60-2.10 (m, 5H), 2.09-1.60 (m, 8H), 1.43-1.00 (m, 6H); ^{19}F NMR (282 MHz, CDCl_3) δ -62.9; ESI MS m/z 609 [$\text{C}_{31}\text{H}_{39}\text{F}_3\text{N}_2\text{O}_5\text{S} + \text{H}$] $^+$.

(39j) Compound 39i-b (103 mg, 168 μmol) and 37% formaldehyde (50 μL , 1.8 mmol) were dissolved in MeOH (2 mL) and stirred for 3 h at room temperature. Sodium cyanoborohydride (16 mg, 252 μmol) was added and the mixture was stirred for 2 h. The reaction was diluted with EtOAc (400 mL), washed with saturated NaHCO_3 (3 \times 150 mL) and brine (100 mL), dried over Na_2SO_4 , filtered, and evaporated. The residue was purified by CombiFlash chromatography (silica, 0-10% $\text{CH}_2\text{Cl}_2/\text{MeOH}$) and then

lyophilized from CH₃CN/H₂O to give title compound (77 mg, 74%) as a white solid: ¹H NMR (300 MHz, CDCl₃) δ 7.90–7.82 (m, 2H), 7.71 (s, 1H), 7.68–7.42 (m, 6H), 4.15–3.92 (m, 3H), 3.80–3.00 (m, 7H), 2.71–2.10 (m, 9H), 1.93–1.40 (m, 9H), 1.17–0.95 (m, 6H); ¹⁹F NMR (282 MHz, CDCl₃) δ -62.9; ESI MS m/z 623 [C₃₂H₄₁F₃N₂O₅S + H]⁺.

Example 40

10 (S*)-1-((1S*,2R*,4R*)-4-(isopropyl(methyl)amino)-2-(phenylsulfonylmethyl)cyclohexyl)-3-((2-(3-(trifluoromethyl)phenyl)-1,3-dioxolan-2-yl)methyl)pyrrolidin-2-one

15 (40a) Diastereomer 39g-a was incorporated into Example 39 (steps 39h-39j) to give the title compound. MS found: (M + H)⁺ = 623.

Example 41

20 (S*)-3-(2-oxo-2-(3-(trifluoromethyl)phenyl)ethyl)-1-((1S*,2R*,4R*)-4-(isopropyl(methyl)amino)-2-(phenylsulfonylmethyl)cyclohexyl)pyrrolidin-2-one

25 (41a) A solution of Example 40 (74.4 mg, 0.120 mmol) in CH₃CN (0.9 mL) and 1 M HCl (0.9 mL) was heated at 60 °C for 5 h. The mixture was diluted with ethyl acetate (500 mL), washed with satd NaHCO₃ (3 × 150 mL) and brine (2 × 100 mL), dried over Na₂SO₄, filtered, and evaporated to dryness. The residue was lyophilized from CH₃CN/H₂O to the title compound as a white solid (70.2 mg, >99): ESI
30 MS m/z 579 [C₃₀H₃₇F₃N₂O₄S + H]⁺.

Example 42

(R*)-3-(2-oxo-2-(3-(trifluoromethyl)phenyl)ethyl)-1-
((1S*,2R*,4R*)-4-(isopropyl(methyl)amino)-2-
(phenylsulfonylmethyl)cyclohexyl)pyrrolidin-2-one

5

(42a) Example 39 was incorporated into Example 41 to give the title compound. MS found: $(M + H)^+ = 579$.

Example 43

10 (R*)-3-(2-hydroxy-2-(3-(trifluoromethyl)phenyl)ethyl)-1-
((1S*,2R*,4R*)-4-(isopropyl(methyl)amino)-2-
(phenylsulfonylmethyl)cyclohexyl)pyrrolidin-2-one
trifluoroacetate

15 (43a) To a solution of Example 42 (19.3 mg, 33.4 μ mol) in MeOH (2 mL) was added sodium borohydride (6 mg, 167 μ mol). After stirring for 1 h, the solvent was removed under vacuum. The residue was dissolved in EtOAc (500 mL), washed with satd NaHCO_3 (3 \times 150 mL) and brine (2 \times 20 100 mL), dried over Na_2SO_4 , filtered, and evaporated to dryness. The residue was purified by preparative TLC (80:12:6:2 EtOAc/ CHCl_3 /MeOH/ NH_4OH). The middle band was lyophilized from $\text{CH}_3\text{CN}/\text{H}_2\text{O}/\text{TFA}$ to give one diastereomer of the title compound 43a-a (7.9 mg, 34%) as a colorless 25 oil. The bottom band was lyophilized from $\text{CH}_3\text{CN}/\text{H}_2\text{O}/\text{TFA}$ to give the second diastereomer of the title compound 43a-b (12.1 mg, 66%) as a colorless oil.

For 43a-a: ^1H NMR (300 MHz, CDCl_3) δ 11.13 (br, s, 1H), 30 8.00–7.89 (m, 2H), 7.75–7.40 (m, 7H), 5.06–4.93 (m, 1H), 4.40–4.29 (m, 1H), 4.10–3.03 (m, 12H), 3.02–2.90 (m, 1H), 2.89–2.50 (m, 5H), 2.41–2.25 (m, 1H), 2.21–1.60 (m, 10H), 1.48–1.40 (m, 3H), 1.38–1.20 (m, 4H); ^{19}F NMR (282

MHz, CDCl₃) δ -62.9, -76.3; ESI MS m/z 581 [C₃₀H₃₉F₃N₂O₄S + H]⁺.

For 43a-b: ¹H NMR (300 MHz, CDCl₃) δ 10.95 (br, s, 1H),
 5 7.98-7.89 (m, 2H), 7.76-7.40 (m, 7H), 4.90-4.80 (m, 1H),
 4.40-4.30 (m, 1H), 4.10-3.90 (m, 1H), 3.89-3.70 (m, 1H),
 3.60-3.48 (m, 1H), 3.42-3.02 (m, 2H), 3.01-2.90 (m, 1H),
 2.89-2.55 (m, 6H), 2.40-2.00 (m, 8H), 1.99-1.55 (m, 4H),
 1.50-1.40 (m, 3H), 1.37-1.20 (m, 5H); ¹⁹F NMR (282 MHz,
 10 CDCl₃) δ -63.0, -76.4; ESI MS m/z 581 [C₃₀H₃₉F₃N₂O₄S + H]⁺.

Example 44

((S*)-3-(2-hydroxy-2-(3-(trifluoromethyl)phenyl)ethyl)-1-
((1S*,2R*,4R*)-4-(isopropyl(methyl)amino)-2-
 15 (phenylsulfonylmethyl)cyclohexyl)pyrrolidin-2-one
trifluoroacetate

(44a) Example 41 was incorporated into Example 43 to give
 the title compound as a mixture of diastereomers. MS
 20 found: (M + H)⁺ = 581.

Example 45

((S*)-1-((1S*,2R*,4R*)-4-(isopropyl(methyl)amino)-2-
(phenylsulfonylmethyl)cyclohexyl)-3-(-2-(methoxyimino)-2-
 25 (3-(trifluoromethyl)phenyl)ethyl)pyrrolidin-2-one
trifluoroacetate

(45a) A stirred mixture of Example 41 (19.7 mg, 34 μ mol),
 methoxylamine•HCl (17 mg, 204 μ mol), NaOAc (17 mg, 204
 30 μ mol), and MeOH (2 mL) was heated at 50 °C for 24 h. The
 solvent was removed under vacuum and the residue was
 dissolved in EtOAc (500 mL). The organic mixture was

washed with satd NaHCO₃ (3 × 100 mL), water (200 mL), and brine (200 mL), dried over Na₂SO₄, filtered, and evaporated. The residue was lyophilized from CH₃CN/H₂O/TFA give the title compound as a mixture of (*E*) and (*Z*) isomers (26.9 mg, 95%): ¹H NMR (500 MHz, CDCl₃) δ 11.03 (s, 1H), 7.97–7.86 (m, 3H), 7.83–7.76 (m, 1H), 7.70–7.63 (m, 1H), 7.62–7.53 (m, 3H), 7.50–7.41 (m, 1H), 4.32–4.20 (m, 1H), 3.99 (s, 3H), 3.95–3.85 (m, 1H), 3.60–3.43 (m, 2H), 3.32–3.20 (m, 1H), 3.15–2.94 (m, 2H), 2.91–2.77 (m, 2H), 2.75–2.65 (m, 3H), 2.63–2.50 (m, 2H), 2.20–1.68 (m, 7H), 1.50–1.40 (m, 3H), 1.35–1.24 (m, 5H); ¹⁹F NMR (282 MHz, CDCl₃) δ -63.1, -76.3; ESI MS *m/z* 608 [C₃₁H₄₀F₃N₃O₄S + H]⁺.1.

15

Example 46

((R*)-1-((1S*,2R*,4R*)-4-(isopropyl(methyl)amino)-2-(phenylsulfonylmethyl)cyclohexyl)-3-(-2-(methoxyimino)-2-(3-(trifluoromethyl)phenyl)ethyl)pyrrolidin-2-one
trifluoroacetate

20

(46a) Example 42 was incorporated into Example 45 to give the title compound as a mixture of (*E*)/(*Z*). ¹H NMR (500 MHz, CDCl₃) δ 10.80 (s, 1H), 7.98–7.85 (m, 3H), 7.81–7.40 (m, 6H), 4.40–4.21 (m, 1H), 4.10–3.84 (m, 3H), 3.83–3.77 (m, 1H), 3.74–3.58 (m, 1H), 3.50–3.15 (m, 3H), 3.14–2.89 (m, 3H), 2.85–2.68 (m, 4H), 2.65–2.49 (m 2H), 2.20–1.98 (m, 5H), 1.93–1.62 (m, 2H), 1.50–1.38 (m, 3H), 1.35–1.20 (m, 5H); ¹⁹F NMR (282 MHz, CDCl₃) δ -63.1, -76.3; ESIMS *m/z* 608 [C₃₁H₄₀F₃N₃O₄S + H]⁺.

30

Example 47

1-((1S*,2R*,4R*)-4-(amino)-2-(phenylsulfonylmethyl)cyclohexyl)-3-(7-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)pyrrolidin-2-one
trifluoroacetate

(47a) 3-(Trifluoromethyl)benzene-1,2-diamine (257 mg, 1.46 mmol) was dissolved in anhydrous DMF (7.5 mL). The mixture was stirred at 0 °C under N₂ as *N*-methyilmorpholine (0.34 mL, 3.09 mmol), compound from Example 24d (456 mg, 1.12 mmol), and benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent, 644 mg, 1.45 mmol) were added sequentially. The mixture was allowed to warm to room temperature and stirred for 14 h, then diluted with EtOAc, washed with 10% aqueous HCl (3×), saturated NaHCO₃ (1×), and brine (1×), dried over Na₂SO₄, filtered and evaporated. The residue was purified by flash column chromatography (silica, 50-100%, EtOAc/hexanes) to provide the two diastereomers of *N*-(2-amino-3-(trifluoromethyl)phenyl)-1-((1S*,2R*,4R*)-4-(azido)-2-(phenylsulfonylmethyl)cyclohexyl)-2-oxopyrrolidine-3-carboxamide as white crushable foams: ESI MS *m/z* 565 [C₂₅H₂₇F₃N₆O₄S + H]⁺.

(47b) The diastereomers from above (47a) (136 mg, 0.241 mmol) and *p*-toluenesulfonic acid monohydrate (35 mg, 0.18 mmol) were stirred in anhydrous toluene (35 mL). The reaction vessel was fitted with a Dean-Stark trap and the mixture was heated to reflux, at which point 10 mL of toluene was removed. The mixture was further heated at reflux for 2 h, then allowed to cool to room temperature,

and the solvent was removed in vacuo. The residue was purified by flash column chromatography (silica, 2-10% MeOH/CH₂Cl₂) to provide 1-((1S*,2R*,4R*)-4-azido-2-(phenylsulfonylmethyl)cyclohexyl)-3-(7-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)pyrrolidin-2-one as a mixture of diastereomers (101 mg, 77%): ¹H NMR (300 MHz, CDCl₃) δ 10.88-10.77 (m, 1H), 7.94-7.76 (m, 3H), 7.65-7.43 (m, 3H), 7.35-7.23 (m, 2H); ESI MS *m/z* 547 [C₂₅H₂₅F₃N₆O₃S + H]⁺.

(47c) To a solution of the above compound (47b) (154 mg, 0.282 mmol) in methanol (7 mL) was added 10% Pd/C (wet, 60 mg). The mixture was hydrogenated (1 atm) for 14 h, then filtered through a pad of diatomaceous earth and concentrated. The residue was purified by preparative TLC (80:18:2 CHCl₃/MeOH/NH₄OH). After concentrating the material in vacuo, the resulting oil was dissolved in CH₃CN/H₂O/TFA and lyophilized to give the title compound (29 mg, 16%) as a white solid and mixture of diastereomers: ESI MS *m/z* 521 [C₂₅H₂₇F₃N₄O₃S + H]⁺.

20

Example 48

1-((1S*,2R*,4R*)-4-(isopropylamino)-2-(phenylsulfonylmethyl)cyclohexyl)-3-(7-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)pyrrolidin-2-one
trifluoroacetate

25

(48a) To a solution of Example 47 (67 mg, 0.13 mmol) in 1,2-dichloroethane (7.3 mL) was added acetone (0.38 mL, 5.2 mmol) and acetic acid (30 μL, 0.51 mmol). The resulting mixture was stirred for 20 min, then sodium triacetoxyborohydride (110 mg, 0.52 mmol) was added.

30

After stirring for 2 h, the mixture was diluted with EtOAc and washed sequentially with saturated aqueous NaHCO₃, water, and brine. The organic phase was dried over Na₂SO₄, filtered, and the solvent was removed in vacuo. The resulting clear, glassy solid was dissolved in CH₃CN/H₂O/TFA and lyophilized to provide the title compound (5.1 mg, 6%) as a white solid and mixture of diastereomers: ESI MS *m/z* 563 [C₂₈H₃₃F₃N₄O₃S + H]⁺.

10

Example 49

1-((1S*,2R*,4R*)-4-(isopropyl(methyl)amino)-2-(phenylsulfonylmethyl)cyclohexyl)-3-(7-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)pyrrolidin-2-one
trifluoroacetate

15

(49a) To a solution of Example 48 (25 mg, 44 μmol) in methanol (1.5 mL) was added a solution of 37% aqueous formaldehyde (14 mL, 178 μmol). The resulting mixture was stirred for 2 h, then sodium cyanoborohydride (5 mg, 67 μmol) was added. After stirring for 3 h, the mixture was treated with saturated aqueous NaHCO₃ and extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, filtered, and the solvent removed in vacuo. The residue was purified by preparative TLC (90:10:1 CHCl₃/MeOH/NH₄OH). After concentrating the material in vacuo, the resulting oil was dissolved in CH₃CN/H₂O/TFA and lyophilized to give the title compound (10 mg, 33%) as a white solid and mixture of diastereomers: ESI MS *m/z* 577 [C₂₉H₃₅F₃N₄O₃S + H]⁺.

30

Example 50

1-((1S*,2R*,4R*)-4-(isopropyl(ethyl)amino)-2-(phenylsulfonylmethyl)cyclohexyl)-3-(7-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)pyrrolidin-2-one
trifluoroacetate

(50a) To a solution of Example 48 (25 mg, 44 μ mol) in 1,2-dichloroethane (3.0 mL) was added acetaldehyde (13 μ L, 222 μ mol) and acetic acid (30 μ L, 0.14 mmol). The resulting mixture was stirred for 20 min, then sodium triacetoxymethylborohydride (38 mg, 0.18 mmol) was added. After stirring for 2 h, the mixture was diluted with EtOAc and washed sequentially with saturated aqueous NaHCO₃, water, and brine. The organic phase was dried over Na₂SO₄, filtered, and the solvent was removed in vacuo. The residue was purified by preparative TLC (70:30 CH₂Cl₂/MeOH). After concentrating the material in vacuo, the resulting oil was dissolved in CH₃CN/H₂O/TFA and lyophilized to provide the title compound (10 mg, 34%) as a white solid and mixture of diastereomers: ESI MS m/z 591 [C₃₀H₃₇F₃N₄O₃S + H]⁺.

Example 51

1-((1S*,2R*,4R*)-4-(Diethylamino)-2-(phenylsulfonylmethyl)cyclohexyl)-3-(7-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)pyrrolidin-2-one
trifluoroacetate

(51a) To a solution of Example 47 (25 mg, 44 μ mol) in 1,2-dichloroethane (2.7 mL) was added acetaldehyde (28 μ L, 492 μ mol) and acetic acid (8 μ L, 96 μ mol). The resulting mixture was stirred for 20 min, then sodium

triacetoxyborohydride (31 mg, 144 μ mol) was added. After stirring for 2 h, the mixture was diluted with EtOAc and washed sequentially with saturated aqueous NaHCO₃, water, and brine. The organic phase was dried over Na₂SO₄,
 5 filtered, and the solvent was removed in vacuo. The residue was purified by preparative TLC (90:10:1 CHCl₃/MeOH/NH₄OH). After concentrating the material in vacuo, the resulting oil was dissolved in CH₃CN/H₂O/TFA and lyophilized to provide the title compound (8.5 mg,
 10 26%) as a white solid and mixture of diastereomers: ESI MS *m/z* 577 [C₂₉H₃₅F₃N₄O₃S + H]⁺.

Example 52

15 1-((1S,2R,4R)-4-(Isopropyl(methyl)amino)-2-(phenylsulfonylmethyl)cyclohexyl)-3-(naphthalen-1-ylamino)pyrrolidin-2-one trifluoroacetate

(52a) (1S*,2R*,4R*)-4-azido-2-benzenesulfonylmethyl-cyclohexylamine trifluoroacetate (see 37c) (2.5 g, 6.3
 20 mmol) was dissolved in DMF (15 mL) prior to the addition of BOP reagent (3.4 g) and N-Boc-L-Met-OH (1.9 g). After cooling to 0 °C, NMM (2.6 mL) was added. The resulting mixture was warmed to rt and was stirred overnight. The solution was diluted with EtOAc, and was washed
 25 successively with brine and sat. NaHCO₃. The organic phase was dried (MgSO₄), filtered, and concentrated. Flash chromatography of the resulting residue gave tert-butyl (S)-1-((1S*,2R*,4R*)-4-azido-2-(phenylsulfonylmethyl)cyclohexylamino)-4-(methylthio)-1-
 30 oxobutan-2-ylcarbamate (2.8 g) as a mixture of diastereomers. MS found: (M + H)⁺ = 526.2.

(52b) The above derivative (52a) was dissolved in MeI (30 mL). After stirring overnight at rt, the solution was concentrated and dried. The resulting material was dissolved in DMF (30 mL) prior to the addition of Cs₂CO₃ (3.5 g). After stirring 3 h, the solution was diluted with EtOAc and was washed with brine. The organic phase was dried (MgSO₄), filtered, and concentrated. Flash chromatography (1:2 up to 2:1 EtOAc/hexane) of the resulting residue provided the bottom diastereomer tert-butyl (S)-1-((1S,2R,4R)-4-azido-2-(phenylsulfonylmethyl)cyclohexyl)-2-oxopyrrolidin-3-ylcarbamate (600 mg). MS found: (M + H)⁺ = 478.3.

(52c) A portion of the above material (52b) (30 mg) was dissolved in MeOH (4 mL) prior to the addition of 10% Pd/C (20 mg). A hydrogen balloon was added and the mixture was stirred. After stirring 2 h, the Pd/C was filtered off and the solvent was concentrated to give tert-butyl (S)-1-((1S,2R,4R)-4-amino-2-(phenylsulfonylmethyl)cyclohexyl)-2-oxopyrrolidin-3-ylcarbamate (29 mg). MS found: (M + H)⁺ = 452.2.

(52d) The above material (52c) was dissolved in dichloroethane (5 mL) prior to the addition of glacial acetic acid (0.2 mL), acetone (1.0 mL), and NaBH(OAc)₃ (20 mg). After 20 h, MeOH (4 mL) was added prior to the addition of 37% formaldehyde in water (1 mL). After 15 min, NaBH₃CN (20 mg) was added. After 1 h, saturated NaHCO₃ was added and some of the MeOH was removed. EtOAc was added and the organic layer was dried, filtered, and concentrated to give tert-butyl (S)-1-((1S,2R,4R)-4-(isopropyl(methyl)amino)-2-

(phenylsulfonylmethyl)cyclohexyl)-2-oxopyrrolidin-3-ylcarbamate (15 mg). MS found: $(M + H)^+ = 508.3$.

(52e) A portion of above material (52b) (160 mg) was
5 dissolved in CH_2Cl_2 (3 mL) and cooled to 0 °C prior to the
addition of TFA (4 mL). After the reaction was warmed to
rt over 1 h, it was concentrated. This material was
dissolved in EtOAc (8 mL) prior to the addition of
saturated Na_2CO_3 solution (3 mL). The organic phase was
10 dried (Na_2CO_3), filtered, and concentrated to afford free
base (S)-3-amino-1-((1S,2R,4R)-4(isopropyl(methyl)amino)-
2-(phenylsulfonylmethyl)cyclohexyl)pyrrolidin-2-one (130
mg). MS found: $(M + H)^+ = 408.2$.

15 (52f) A portion of the above material (52e) (30 mg, 74
 μmol), sodium *tert*-butoxide (14 mg, 140 μmol), and
toluene (0.7 mL) were placed in a reaction tube equipped
with a stir bar and screw cap. After passing argon
through the reaction mixture for 2 min, BINAP (8 mg, 13
20 μmol), $\text{Pd}_2(\text{dba})_3$ (4 mg, 4 μmol) and 1-bromonaphthalene (9
 μL , 61 μmol) were added sequentially. The mixture was
evacuated again with argon, then sealed and heated to 85
°C overnight. After cooling to room temperature, the
mixture was diluted with ether, filtered through a pad of
25 diatomaceous earth, and concentrated. The residue was
purified by semi-preparative HPLC, then lyophilized to
provide the title compound (9.5 mg) as a gray solid and
mixture of diastereomers. ESI MS m/z 534 [$\text{C}_{31}\text{H}_{39}\text{N}_3\text{O}_3\text{S} + \text{H}$] $^+$.

Example 53

3-(Benzo[b]thiophen-3-ylamino)-1-((1S,2R,4R)-4-
(isopropyl(methyl)amino)-2-
(phenylsulfonylmethyl)cyclohexyl)pyrrolidin-2-one
trifluoroacetate

(53a) A portion of the above amine (52e) (27 mg, 66 μmol), sodium *tert*-butoxide (13 mg, 130 μmol), and toluene (0.7 mL) were placed in a reaction tube equipped with a stir bar and screw cap. After passing argon through the reaction mixture for 2 min, 2-(di-*t*-butylphosphino)biphenyl (12 mg, 40 μmol), $\text{Pd}_2(\text{dba})_3$ (6 mg, 7 μmol) and 3-bromothianaphthene (18 μL , 130 μmol) were added sequentially. The mixture was evacuated again with argon, then sealed and stirred overnight. The mixture was diluted with ether, filtered through a pad of diatomaceous earth, and concentrated. The residue was purified by preparative TLC (9:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$), then lyophilized to provide the title compound (4.4 mg) as a light yellow solid and mixture of diastereomers. ESI MS m/z 540 $[\text{C}_{29}\text{H}_{37}\text{N}_3\text{O}_3\text{S}_2 + \text{H}]^+$.

Example 54

(S)-3-(6-chloroquinazolin-4-ylamino)-1-((1S,2R,4R)-4-
(isopropyl(methyl)amino)-2-
(phenylsulfonylmethyl)cyclohexyl)pyrrolidin-2-one
trifluoroacetate

(54a) The above amine (52e) (20 mg), triethylamine (0.03 mL), and 4,6-dichloroquinazoline (15 mg) were dissolved in EtOH (2 mL) and placed in a microwave. The reaction was heated at 100 °C for 22 min. The solution was

filtered and the filtrate was subjected to reverse phase HPLC purification (gradient elution, water/acetonitrile/TFA) to provide the title compound (11.3 mg). MS found: $(M+H)^+ = 570.2$.

5

Example 55

(S)-3-(6,8-dichloroquinazolin-4-ylamino)-1-((1S,2R,4R)-4-(isopropyl(methyl)amino)-2-(phenylsulfonylmethyl)cyclohexyl)pyrrolidin-2-one
trifluoroacetate

10

(55a) 4,6,8-Trichloroquinazoline was incorporated into Example 54 to give the title compound. MS found: $(M+H)^+ = 604.2$.

15

Example 56

3,5-Dichloro-N-((S)-1-((1S,2R,4R)-4-(isopropyl(methyl)amino)-2-(phenylsulfonylmethyl)cyclohexyl)-2-oxopyrrolidin-3-yl)benzamide
trifluoroacetate

20

(56a) Amine 52e (15 mg) was dissolved in DMF (2 mL) prior to the addition of diisopropylethylamine (0.02 mL) and 3,5-dichlorobenzoic acid (10 mg). After cooling to 0 °C, BOP reagent (19 mg) was added. The resulting mixture was warmed to rt and was stirred overnight. The solution was diluted with EtOAc and was washed with sat. NaHCO_3 . The organic phase was dried (MgSO_4), filtered, and concentrated. Reverse phase HPLC purification (gradient elution, water/acetonitrile/TFA) of the resulting residue provided the title compound (1.0 mg). MS found: $(M+H)^+ = 580$.

25

30

Example 57

5 N-((S)-1-((1S,2R,4R)-4-(isopropyl(methyl)amino)-2-
 (phenylsulfonylmethyl)cyclohexyl)-2-oxopyrrolidin-3-yl)-
 3-(trifluoromethoxy)benzamide trifluoroacetate

(57a) 3-Trifluoromethoxybenzoic acid was incorporated into Example 56 to give the title compound. MS found: (M + H)⁺ = 596.2.

10

Example 58

15 3-((E)-3(R*)-(trifluoromethyl)styryl)-1-((1S*,2R*,4R*)-4-
 (isopropyl(methyl)amino)-2-
 (phenylsulfonylmethyl)cyclohexyl)pyrrolidin-2-one
 trifluoroacetate

(58a) Compound 39g-b (2.0 g) was dissolved in CH₃CN (25 mL) and 1 M HCl (25 mL) was stirred at 60 °C for 6 h. The mixture was diluted with ethyl acetate (500 mL),
 20 washed with satd NaHCO₃ (3 × 150 mL) and brine (2 × 100 mL), dried over Na₂SO₄, filtered, and evaporated to dryness to give 1-((1S*,2R*,4R*)-4-azido-2-(phenylsulfonylmethyl)cyclohexyl)-3(R*)-(3-(trifluoromethyl)benzoyl)pyrrolidin-2-one as a white
 25 solid (1.85 g). ESI MS m/z 549 [C₂₆H₂₇F₃N₄O₄S + H]⁺.

(58b) A solution of LiHMDS (5.06 mL, 1 M in hexanes) in THF (50.6 mL) was cooled to -78 °C. A precooled solution of compound (58a) (2.80 g, 5.06 mmol) in THF (25 mL) was
 30 added dropwise. The mixture was stirred for 1 h at -78 °C then a precooled solution of 2-[(N,N-bistrifluoromethylsulfonyl)amino]-5-chloropyridine (2.90

g, 7.38 mmol) in THF (30 mL) was added. After 90 min, the reaction was warmed to -5 °C and stirred for 2 h. The mixture was diluted with EtOAc (800 mL), washed with satd NH₄Cl (3 × 150 mL) and brine (100 mL), dried over Na₂SO₄, filtered, and concentrated, filtering off the 2-amino-5-chloropyridine byproduct. The filtrate was evaporated to dryness, and purified by flash chromatography (silica-gel, 0-100% EtOAc/hexanes) to give 2-(1-((1S*,2R*,4R*)-4-azido-2-(phenylsulfonylmethyl)cyclohexyl)-2-oxopyrrolidin-3-yl)-1-(3(R*)-(trifluoromethyl)phenyl)vinyl trifluoromethanesulfonate (2.30 g, 67%) as a white solid: ¹H NMR (300 MHz, CDCl₃) δ 7.92-7.83 (m, 2H), 7.78-7.50 (m, 7H), 6.07 (d, *J* = 9.0 Hz, 1H), 4.00-3.89 (m, 5H), 3.22 (dd, *J* = 14.7, 3.4 Hz, 1H), 2.80-2.45 (m, 2H), 2.18-1.60 (m, 9H); ¹⁹F NMR (282 MHz, CDCl₃) δ -63.4 (3F), -74.1 (3F).

(58c) A mixture of Pd(PPh₃)₄ (25.5 mg, 22 μmol) and LiCl (140 mg, 3.29 mmol) in THF (3.28 mL) was stirred under argon atmosphere. A solution of compound 58b (750 mg, 1.03 mmol) in THF (3.68 mL) was added, followed by slow addition of tributyltin hydride (μL, 1.32 mmol). The mixture was stirred 4 h at room temperature, diluted with EtOAc (500 mL), washed with satd NaHCO₃ (3 × 100 mL), brine (200 mL), dried over Na₂SO₄, filtered, and evaporated. The residue was purified by flash chromatography (silica gel with a plug of KF, 0-80% EtOAc/hexanes) to give the 3(R*)-((E)-3-(trifluoromethyl)styryl)-1-((1S*,2R*,4R*)-4-azido-2-(phenylsulfonylmethyl)cyclohexyl)pyrrolidin-2-one (347

mg, 59%) as white solids. ESI MS m/z 533 [$C_{26}H_{27}F_3N_4O_3S + H$] $^+$.

(58d) A mixture of 58c (117 mg, 220 μ mol) and
 5 triphenylphosphine (115 mg, 440 μ mol) in THF (10 mL) was
 stirred at room temperature for 23 h. Water (2 mL) was
 added and the mixture was stirred for 2 d. The volume
 was reduced under vacuum and the residue was dissolved in
 EtOAc (500 mL). The mixture was extracted with 1 M HCl
 10 (3 \times 150 mL), and the aqueous layer was made basic with 6
 N NaOH, then extracted with EtOAc (3 \times 150 mL). The
 organic layer was dried over Na_2SO_4 , filtered, and
 evaporated to give crude free amine. This material (24
 mg, 47 μ mol), acetone (200 μ L, 2.73 mmol), and acetic
 15 acid (20 μ L, 348 μ mol) in 1,2-dichloroethane (4 mL) was
 stirred for 3 min, then treated with sodium
 triacetoxymethylborohydride (20 mg, 95 μ mol). After stirring
 the mixture for 1 h, the solvent was removed under
 vacuum. The residue was dissolved in MeOH (4 mL), then
 20 37% aqueous formaldehyde (400 μ L) and sodium
 cyanoborohydride (4.5 mg, 71 μ mol) were added. The
 mixture was stirred 18 h, and the solvent was removed
 under vacuum. The residue was purified by semi-
 preparative HPLC, and the product lyophilized from
 25 $CH_3CN/H_2O/TFA$ to give the title compound (23.8 mg). ESI MS
 m/z 563 [$C_{30}H_{37}F_3N_2O_3S + H$] $^+$.

Example 59

30 1-((1S*,2R*,4R*)-4-(isopropyl(methyl)amino)-2-
(phenylsulfonylmethyl)cyclohexyl)-3(R*)-((E/Z)-2-(3-
(trifluoromethyl)phenyl)prop-1-enyl)pyrrolidin-2-one
trifluoroacetate

(59a) A suspension of copper bromide•dimethylsulfide (1.03 g, 5.01 mmol) in THF (10 mL) was cooled to -78 °C. Methylmagnesium bromide (3 M in ether, 3.34 mL, 10 mmol) was added dropwise, then the mixture was removed from the dry ice bath and THF (3 mL) was added. After stirring for 7 min, the mixture was cooled to -78 °C. A solution of compound 58b (569 mg) in THF (11 mL) was added dropwise and the reaction mixture was stirred for 2 h. The mixture was diluted with EtOAc (500 mL), washed with satd NH₄Cl (3 × 100 mL) and brine (200 mL), dried over Na₂SO₄, filtered, and evaporated. The residue was purified by flash column chromatography (silica-gel, 0-70%, THF/hexanes) to provide 1-((1S*,2R*,4R*)-4-azido-2-(phenylsulfonylmethyl)cyclohexyl)-3(R*)-((E/Z)-2-(3-(trifluoromethyl)phenyl)prop-1-enyl)pyrrolidin-2-one (436 mg). ESI MS *m/z* 547 [C₂₇H₂₉F₃N₄O₃S + H]⁺.

(59b) The above material 59a was incorporated into Example 58 (step 58d) to give the title compound. MS found: (M + H)⁺ = 577.

Example 60

N-(1-((1S,2R,4R)-4-(isopropyl(methyl)amino)-2-(phenylsulfonylmethyl)cyclohexyl)-2-oxopyrrolidin-3(R)-yl)benzamide trifluoroacetate

(60a) Benzoic acid was incorporated into Example 56 to give the title compound. MS found: (M + H)⁺ = 512.

Example 61

N-((S)-1-((1S,2R,4R)-4-(Isopropyl(methyl)amino)-2-(phenylsulfonylmethyl)cyclohexyl)-2-oxopyrrolidin-3-yl)-3,5-bis(trifluoromethyl)benzamide trifluoroacetate

5

(61a) (1S,2R)-cis-2-Methoxycarbonyl-cyclohex-4-ene-1-carboxylic acid (66.0 g, see Bolm et al. J. Org. Chem. **2000**, 65, 6984-6991) was dissolved in dry acetone (815 mL) prior to the addition of triethylamine (43.4 g).

10 This solution was cooled to 0 °C and ethyl chloroformate (46.7 g) was added. The resulting solution was stirred 1 h before NaN₃ (35.0 g) was added. The cooling bath was removed, and the reaction was warmed to rt overnight. All solid material was removed by filtration, and the
15 solution was partially concentrated. Water was slowly added and the organic layer was separated. The aqueous layer was extracted with ether. The combined organic layers were washed with water and brine before they were dried, filtered, and concentrated. The resulting oil
20 (66.1 g) was dissolved in benzene (800 mL) and was warmed to a gentle reflux. After 4 h, the solution was cooled back to rt. Benzyl alcohol (37.5 g) and *p*-TsOH (1.5 g) were added, and the solution was warmed back to a gentle reflux overnight. After cooling to rt, the reaction was
25 washed with NaHCO₃ and brine, dried, filtered, and concentrated to give (1R,6S)-6-benzyloxycarbonylamino-cyclohex-3-enecarboxylic acid methyl ester (97.7 g). MS found: (M + H)⁺ = 290.2.

30 (61b) A sample of (1R,6S)-6-benzyloxycarbonylamino-cyclohex-3-enecarboxylic acid methyl ester (91.4 g) was dissolved in MeOH (500 mL) prior to the dropwise addition of NaOH (25.3 g) in water (95 mL). After 3 h, the solution was partially concentrated and an Et₂O/water
35 mixture was added. The aqueous layer was separated and was acidified (pH ~ 2) with concentrated HCl. The resulting mixture was extracted with EtOAc. The combined

organic layers were washed with water and brine before they were dried, filtered, and concentrated to give (1R,6S)-6-benzyloxycarbonylamino-cyclohex-3-enecarboxylic acid (72.7 g). MS found: $(M + H)^+ = 276.2$.

5

(61c) A sample of (1R,6S)-6-benzyloxycarbonylamino-cyclohex-3-enecarboxylic acid (72 g) was dissolved in CH_2Cl_2 (750 mL) prior to the addition of CDI (50.9 g). After 2.5 h water was added, and the solution was
10 extracted with CH_2Cl_2 . The combined organic layers were dried, filtered, and concentrated. The resulting material was dissolved in CH_2Cl_2 and ammonia gas was bubbled through the solution for 1.5 h. After stirring overnight, the majority of the solvent was removed and
15 Et_2O was added. The product precipitated as a white solid and was collected to give (1R,6S)-6-carbamoylcyclohex-3-enyl)carbamic acid benzyl ester (61.5 g). MS found: $(M+H)^+ = 275.3$.

20 (61d) A sample of (1R,6S)-6-carbamoylcyclohex-3-enyl)-carbamic acid benzyl ester (30.7 g) was dissolved in THF (1100 mL) and NMP (220 mL). At $-78^\circ C$, 2.3M *n*-BuLi (96.3 mL) was added dropwise. After 2 h, a solution of Boc_2O (24.4 g) in THF (40 mL) was added dropwise. This
25 solution was stirred 1.2 h before it was quenched with a saturated NH_4Cl solution. Water and Et_2O were added. The organic layer was filtered then washed with water, brine, dried, filtered, and concentrated. Flash chromatography of the resulting residue gave (1R,6S)-(6-tert-
30 butoxycarbonylamino-carbonyl-cyclohex-3-enyl)-carbamic acid benzyl ester (29.2 g). MS found: $(M + Na)^+ = 397.4$.

(61e) A sample of (1R,6S)-(6-tert-butoxycarbonyl-aminocarbonylcyclohex-3-enyl)carbamic acid benzyl ester
35 (29.0 g) was dissolved in THF (1290 mL). This was cooled in an ice/brine bath prior to the addition of *n*-BuLi (1.5 mL, 2.4M). After 30 min, iodine (59.0 g) was added in a

single portion. The bath was removed, and the reaction was warmed to rt overnight. The resulting solution was quenched with saturated thiosulfate solution. Water and EtOAc were added. The organic layer was washed with
5 water, brine, dried, filtered, and concentrated. The resulting slurry was diluted with Et₂O and (1*R*,2*S*,4*S*,5*R*)-2-benzyloxycarbonyl-amino-4-iodo-7-oxo-6-aza-bicyclo[3.2.1]octane-6-carboxylic acid tert-butyl ester (22.8 g) was collected by vacuum filtration. MS found:
10 (M - C₅H₈O₂ + H)⁺ = 401.1.

(61f) A sample of (1*R*,2*S*,4*S*,5*R*)-2-benzyloxycarbonylamino-4-iodo-7-oxo-6-aza-bicyclo[3.2.1]octane-6-carboxylic acid tert-butyl ester (43.3 g) was dissolved in benzene (580
15 mL) prior to the addition of Bu₃SnH (27.8 g) and AIBN (0.7 g). The resulting mixture was warmed to a gentle reflux for 3 h. After cooling, the solvent was removed and hexane was added. The resulting white solid was collected by vacuum filtration to give (1*R*, 2*S*, 5*R*)-2-benzyloxycarbonylamino-7-oxo-6-aza-bicyclo[3.2.1]octane-6-carboxylic acid tert-butyl ester (29.5 g). MS found:
20 (M + Na)⁺ = 397.4.

(61g) A solution of (1*R*,2*S*,5*R*)-2-benzyloxycarbonylamino-7-oxo-6-aza-bicyclo[3.2.1]octane-6-carboxylic acid tert-butyl ester (10.21 g, 27.3 mmol) in tetrahydrofuran (200
25 mL) was treated with water (40 mL) and then with sodium borohydride (5.16 g, 136 mmol). The mixture was stirred at room temperature for 2 h, then was treated with
30 saturated aqueous sodium bicarbonate and stirred until the bubbling subsided. The mixture was extracted three times with ethyl acetate. The combined extracts were washed with saturated aqueous sodium chloride, dried over sodium sulfate, and concentrated under vacuum. The
35 residue was recrystallized from ethyl acetate-hexane to provide (1*R*,3*R*,4*S*)-(4-benzyloxycarbonylamino-3-

hydroxymethylcyclohexyl)carbamic acid tert-butyl ester as a white solid (6.8 g); additional product (2.1 g) was obtained by flash column chromatography of the residue from concentration of the mother liquors, eluting with
5 40%, then 50% ethyl acetate-hexane. MS found: $(M + H)^+ = 379.28$.

(61h) A solution of (1R,3R,4S)-(4-benzyloxycarbonylamino-3-hydroxymethylcyclohexyl)carbamic acid tert-butyl ester
10 (3.49 g, 9.22 mmol) in tetrahydrofuran (40 mL) was treated with diphenyl disulfide (4.03 g, 18.4 mmol) and tri-n-butylphosphine (4.6 mL, 18.4 mmol) and the solution was heated at reflux for 17 h. The mixture was cooled and concentrated under vacuum, and the residue was purified
15 by flash column chromatography, eluting with 10%, then 20% ethyl acetate-hexane, to provide (1S,2R,4R)-(4-tert-butoxycarbonylamino-2-phenyl-sulfanylmethylcyclohexyl)-carbamic acid benzyl ester (4.37 g) as a white glassy solid. MS found: $(M + H)^+ = 471.65$.

20 (61i) A solution of (1S,2R,4R)-(4-tert-butoxycarbonylamino-2-phenylsulfanylmethylcyclohexyl)carbamic acid benzyl ester (4.37 g, 9.22 mmol) in 2-propanol (100 mL) was treated with a solution of Oxone (11.34 g, 18.44
25 mmol) in water (60 mL). The mixture was stirred at room temperature for 18 h, then was diluted with water and extracted with ethyl acetate. The organic phases were washed with water, then with brine, then were dried over sodium sulfate and concentrated under vacuum to provide
30 (1S,2R,4R)-(2-benzene-sulfonylmethyl-4-tert-butoxycarbonylamino-cyclohexyl)-carbamic acid benzyl ester (4.77 g) as a white glassy solid, used without further purification. MS found: $(M + H)^+ = 503.6$.

(61j) A mixture of (1S,2R,4R)-(2-benzene-sulfonylmethyl-4-tert-butoxycarbonylamino)cyclohexyl)carbamic acid benzyl ester (2.96 g, 5.9 mmol) and 20% palladium hydroxide on charcoal (Pearlman's catalyst, 2.0 g) in methanol (100 mL) was stirred under one atmosphere of hydrogen at room temperature for 16.5 h. The mixture was filtered through Celite, and the solids were washed with methanol. The filtrate was concentrated under vacuum and the residue was dissolved in dichloromethane. The solution was dried over sodium sulfate and concentrated under vacuum to provide (1R,3R,4S)-(4-amino-3-benzenesulfonylmethylcyclohexyl)-carbamic acid tert-butyl ester (2.02 g) as a white glassy solid, used without further purification. MS found: $(M + H)^+ = 369.62$.

(61k) This material (61j) was incorporated into Steps 52a to 52b (substituting N-Cbz-L-Met-OH for N-Boc-L-Met-OH) to give tert-butyl (1R,3R,4S)-4-((S)-2-oxo-3-(2-phenylacetamido)pyrrolidin-1-yl)-3-(phenylsulfonylmethyl)cyclohexylcarbamate. MS found: $(M + H)^+ = 586.6$.

(61l) A portion of above material (61k) (2.0 g) was dissolved in CH_2Cl_2 (5 mL) and cooled to 0 °C prior to the addition of TFA (7 mL). After the reaction was warmed to rt over 1 h, it was concentrated and dried. This material, acetone (993 mg), and acetic acid (1 mL) in 1,2-dichloroethane (15 mL) was stirred for 3 min, then treated with sodium triacetoxyborohydride (1.4 g). After stirring for 20 h, MeOH (10 mL) was added followed by 37% aqueous formaldehyde (2 mL) and sodium cyanoborohydride (427 mg) were added. The mixture was stirred 3 h, and the solvent was removed under vacuum. The residue was dissolved in EtOAc (200 mL), washed with saturated NaHCO_3 , dried over Mg_2SO_4 , filtered, and evaporated to provide N-((S)-1-((1S,2R,4R)-4-(isopropyl(methyl)amino)-2-

(phenylsulfonylmethyl)cyclohexyl)-2-oxopyrrolidin-3-yl)-
2-phenylacetamide (2.7 g). MS found: $(M + H)^+ = 542.2$.

5 (61m) A portion of above material (61l) (300 mg) was
dissolved in 33%(wt) HBr/AcOH (3 mL). After 30 min, Et₂O
(20 mL) was added and a white solid precipitated from
solution. This solid was collected to give (S)-3-amino-
1-((1S,2R,4R)-4-(isopropyl(methyl)amino)-2-
(phenylsulfonylmethyl)cyclohexyl)pyrrolidin-2-one
10 dihydrogen bromide (300 mg). MS found: $(M + H)^+ = 408.2$.

15 (61n) The above material (61m) was dissolved in EtOAc (8
mL) prior to the addition of saturated Na₂CO₃ solution (3
mL). The organic phase was dried (Na₂CO₃), filtered, and
concentrated to afford free base (S)-3-amino-1-
((1S,2R,4R)-4-(isopropyl(methyl)amino)-2-
(phenylsulfonylmethyl)cyclohexyl)pyrrolidin-2-one (210
mg). MS found: $(M + H)^+ = 408.2$.

20 (61o) A portion of the above material (61n) (30 mg) was
dissolved in DMF (1 mL) prior to the addition of NMM
(29.3 mg) and 3,5-ditrifluoromethylbenzoic acid (16.2
mg). After cooling to 0 °C, BOP reagent (38 mg) was
added. The resulting mixture was warmed to rt and was
25 stirred overnight. The solution was diluted with EtOAc
and was washed with sat. NaHCO₃. The organic phase was
dried (MgSO₄), filtered, and concentrated. Reverse phase
HPLC purification (gradient elution,
water/acetonitrile/TFA) of the resulting residue provided
30 the title compound (X.0 mg). MS found: $(M + H)^+ = 648$.

Example 62

2-Amino-N-(1-((1S,2R,4R)-4-(isopropyl(methyl)amino)-2-(phenylsulfonylmethyl)cyclohexyl)-2-oxopyrrolidin-3(R)-yl)-5-(trifluoromethoxy)benzamide trifluoroacetate

5

(62a) 2-(*tert*-Butoxycarbonylamino)-5-

(trifluoromethoxy)benzoic acid was incorporated into Step (61o) to give the *tert*-butyl 2-((1-((1S,2R,4R)-4-(isopropyl(methyl)amino)-2-

10 (phenylsulfonylmethyl)cyclohexyl)-2-oxopyrrolidin-3(R)-yl)carbamoyl)-4-(trifluoromethoxy)phenylcarbamate. MS found: (M + H)⁺ = 711.

(62b) The above material (62a) (20 mg) was dissolved in

15 CH₂Cl₂ (2 mL) and cooled to 0 °C prior to the addition of TFA (4 mL). After the reaction was warmed to rt over 30 min, it was concentrated and dried to provide the title compound. MS found: (M + H)⁺ = 611.

20

Example 63

(R)-1-((1S,2R,4R)-4-(isopropyl(methyl)amino)-2-(phenylsulfonylmethyl)cyclohexyl)-3-(6-(trifluoromethyl)quinolin-4-ylamino)pyrrolidin-2-one
trifluoroacetate

25

(63a) Compound (61n) (30 mg), sodium *tert*-butoxide (10.1 mg), 4-chloro-6-trifluoromethylquinoline (25 mg), and toluene (1.3 mL) were placed in a reaction vial equipped with a stir bar and screw cap. After passing argon
30 through the reaction mixture for 2 min, acetato(2'-di-*t*-butylphosphino-1,1'-biphenyl-2-yl)palladium(II) (1 mg) was added and the solution was heated to 80 °C overnight.

After cooling to room temperature, the mixture was concentrated and then dissolved in MeOH before it was filtered. The filtrate was purified by reverse phase HPLC purification (gradient elution,
 5 water/acetonitrile/TFA) to provide two diastereomers. The first diastereomer off the HPLC being the title compound (10.0 mg). MS found: $(M+H)^+ = 603.2$.

Example 64

10 (S)-1-((1S,2R,4R)-4-(isopropyl(methyl)amino)-2-
(phenylsulfonylmethyl)cyclohexyl)-3-(6-
(trifluoromethyl)quinolin-4-ylamino)pyrrolidin-2-one
trifluoroacetate

15 (64a) The second diastereomer off the HPLC from Example 63 is the title compound. MS found: $(M+H)^+ = 603.2$.

Example 65

20 (R)-1-((1S,2R,4R)-4-(isopropyl(methyl)amino)-2-
(phenylsulfonylmethyl)cyclohexyl)-3-(7-
(trifluoromethyl)quinolin-4-ylamino)pyrrolidin-2-one
trifluoroacetate

(65a) 4-Chloro-7-trifluoromethylquinoline was
 25 incorporated into Example 63 to give the title compound as the first diastereomer. MS found: $(M+H)^+ = 603.2$.

Example 66

30 (S)-1-((1S,2R,4R)-4-(isopropyl(methyl)amino)-2-
(phenylsulfonylmethyl)cyclohexyl)-3-(7-

(trifluoromethyl)quinolin-4-ylamino)pyrrolidin-2-one
trifluoroacetate

(66a) The second diastereomer off the HPLC from Example
 5 65 is the title compound. MS found: $(M + H)^+ = 603.2$.

Example 67

3-(2-(Phenyl)phenylamino)-1-((1S,2R,4R)-4-
(isopropyl(methyl)amino)-2-
 10 (phenylsulfonylmethyl)cyclohexyl)pyrrolidin-2-one
trifluoroacetate

(67a) 2-Bromo-biphenyl was incorporated into Example 63
 to give the title compound as a mixture of diastereomers.
 15 MS found: $(M + H)^+ = 560.3$.

Example 68

3-(3,5-Bis(trifluoromethyl)phenylamino)-1-((1S,2R,4R)-4-
(isopropyl(methyl)amino)-2-
 20 (phenylsulfonylmethyl)cyclohexyl)pyrrolidin-2-one
trifluoroacetate

(68a) 3,5-Ditrifluoromethyl-1-bromobenzene was
 incorporated into Example 63 to give the title compound
 25 as a mixture of diastereomers. MS found: $(M + H)^+ =$
 620.2.

Example 69

1-((1S,2R,4R)-4-(Isopropyl(methyl)amino)-2-
 30 (phenylsulfonylmethyl)cyclohexyl)-3-(2-

(trifluoromethyl)phenylamino)pyrrolidin-2-one
trifluoroacetate

(69a) 2-Trifluoromethyl-1-bromobenzene was incorporated
 5 into Example 63 to give the title compound as a mixture
 of diastereomers. MS found: $(M + H)^+ = 552.3$.

Example 70

1-((1S,2R,4R)-4-(Isopropyl(methyl)amino)-2-
 10 (phenylsulfonylmethyl)cyclohexyl)-3-(2-
methoxyphenylamino)pyrrolidin-2-one trifluoroacetate

(70a) 2-Methoxy-1-bromobenzene was incorporated into
 Example 63 to give the title compound as a mixture of
 15 diastereomers. MS found: $(M + H)^+ = 568.3$.

Example 71

1-((1S,2R,4R)-4-(Isopropyl(methyl)amino)-2-
 (phenylsulfonylmethyl)cyclohexyl)-3-(3-
 20 (trifluoromethyl)phenylamino)pyrrolidin-2-one
trifluoroacetate

(71a) 3-Trifluoromethyl-1-bromobenzene was incorporated
 into Example 63 to give the title compound as a mixture
 25 of diastereomers. MS found: $(M + H)^+ = 552.3$.

Example 72

1-((1S,2R,4R)-4-(Isopropyl(methyl)amino)-2-
 (phenylsulfonylmethyl)cyclohexyl)-3-(4-
 30 (trifluoromethyl)phenylamino)pyrrolidin-2-one
trifluoroacetate

(72a) 4-Trifluoromethyl-1-bromobenzene was incorporated into Example 63 to give the title compound as a mixture of diastereomers. MS found: $(M + H)^+ = 552.3$.

5

Example 73

3-Chloro-N-((S)-1-((1S,2R,4R)-4-(isopropyl(methyl)amino)-2-(phenylsulfonylmethyl)cyclohexyl)-2-oxopyrrolidin-3-yl)benzamide trifluoroacetate

10

(73a) 3-Chlorobenzoic acid was incorporated into Step (61o) to give the title compound. MS found: $(M + H)^+ = 546$.

15

Example 74

3-Fluoro-N-((S)-1-((1S,2R,4R)-4-(isopropyl(methyl)amino)-2-(phenylsulfonylmethyl)cyclohexyl)-2-oxopyrrolidin-3-yl)-5-(trifluoromethyl)benzamide trifluoroacetate

20

(74a) 3-Fluoro-5-trifluoromethylbenzoic acid was incorporated into Step (61o) to give the title compound. MS found: $(M + H)^+ = 598$.

Example 75

25

tert-Butyl (1R,3R,4S)-4-((S)-2-oxo-3-(3-(trifluoromethyl)benzamido)pyrrolidin-1-yl)-3-(phenylsulfonylmethyl)cyclohexylcarbamate

(75a) Compound (61k) (1.0 g) was dissolved in MeOH (15 mL) prior to the addition 10% Pd/C (200 mg). A hydrogen

30

balloon was attached and the solution was stirred 18 h. The mixture was filtered through Celite, and the solids were washed with methanol. The filtrate was concentrated to provide tert-butyl (1R,3R,4S)-4-((S)-3-amino-2-oxopyrrolidin-1-yl)-3-(phenylsulfonylmethyl)cyclohexylcarbamate (980 mg) as a white glassy solid, used without further purification. MS found: $(M + H)^+ = 452.2$.

(75b) The above material (75a, 980 mg) was dissolved in DMF prior to the addition of 4-methylmorpholine (NMM) (481.5 mg) and 3-trifluoromethyl-benzoic acid (581.7 mg). After cooling to 0 °C, BOP reagent (1.4 g) was added. The resulting mixture was warmed to rt and was stirred overnight. EtOAc was added along with saturated NaHCO₃ solution. The EtOAc layer was washed with NaHCO₃ solution (aq), dried (MgSO₄), filtered, and concentrated. Flash chromatography of the resulting residue provided the title compound (978 mg). MS found: $(M + H)^+ = 624.7$.

Example 76

N-((S)-2-Oxo-1-((1S,2R,4R)-4-(phenylamino)-2-(phenylsulfonylmethyl)cyclohexyl)pyrrolidin-3-yl)-3-(trifluoromethyl)benzamide trifluoroacetate

(76a) Example 75 (970 mg) was dissolved in CH₂Cl₂ (2 mL) and cooled to 0 °C prior to the addition of TFA (7 mL). After the reaction was warmed to rt over 1 h, it was concentrated and dried to provide N-((S)-1-((1S,2R,4R)-4-amino-2-(phenylsulfonylmethyl)cyclohexyl)-2-oxopyrrolidin-3-yl)-3-(trifluoromethyl)benzamide trifluoroacetate (1.01 g). MS found: $(M + H)^+ = 524.1$.

(76b) The above material (76b) was dissolved in EtOAc (10 mL) prior to the addition of saturated Na₂CO₃ solution (4 mL). The organic phase was dried (Na₂CO₃), filtered, and concentrated to afford free base N-((S)-1-((1S,2R,4R)-4-amino-2-(phenylsulfonylmethyl)cyclohexyl)-2-oxopyrrolidin-3-yl)-3-(trifluoromethyl)benzamide (850 mg). MS found: (M + H)⁺ = 524.1.

(76c) A portion of compound (76b) (10 mg), sodium *tert*-butoxide (3.5 mg), bromobenzene (0.1 mL), and toluene (1.0 mL) were placed in a reaction vial equipped with a stir bar and screw cap. After passing argon through the reaction mixture for 2 min, [Pd(μ -Br)(*t*-Bu₃P)]₂ (1 mg) was added and the solution was heated to 80 °C overnight. After cooling to room temperature, the mixture was concentrated and then dissolved in MeOH before it was filtered. The filtrate was purified by reverse phase HPLC purification (gradient elution, water/acetonitrile/TFA) to provide the title compound (4.5 mg). MS found: (M+ H)⁺ = 600.1.

Example 77

N-(2-Oxo-1-((1S,2R,4R)-2-(phenylsulfonylmethyl)-4-(pyridin-4-ylamino)cyclohexyl)pyrrolidin-3-yl)-3-(trifluoromethyl)benzamide trifluoroacetate

(77a) Sodium-*tert*-butoxide (11 mg, 0.114 mmol), 3-bromopyridine (14 mg, 0.086 mmol), and precatalyst acetato(2-di-*t*-butylphosphino-1,1-biphenyl-2-yl)palladium(II) (2 mg, 0.004 mmol) were added to compound (76b) (30 mg) in toluene (2 mL), degassed by

bubbling argon for 30 min. The vial was sealed under argon and the reaction heated overnight at 90 °C. Brine (1 mL) was added to quench the reaction and the mixture was evaporated to dryness *in vacuo*. The crude residue
 5 was taken up in acetonitrile/water (1:1, 2.5 mL) and purified by C18 HPLC (acetonitrile/water 0.05%TFA) to give the title compound (6.7 mg) as a mixture of diastereomers. ESI MS *m/z* 601 [C₃₀H₃₁F₃N₄O₄S + H]⁺.

10

Example 78

N-(2-Oxo-1-((1S,2R,4R)-2-(phenylsulfonylmethyl)-4-(thiazol-2-ylamino)cyclohexyl)pyrrolidin-3-yl)-3-(trifluoromethyl)benzamide trifluoroacetate

15 (78a) 2-Bromothiazole was incorporated into Example 77 to give the title compound as a mixture of diastereomers. MS found: (M + H)⁺ = 607.

Example 79

20

Methyl (1R,3R,4S)-4-((S)-2-oxo-3-(3-(trifluoromethyl)benzamido)pyrrolidin-1-yl)-3-(phenylsulfonylmethyl)cyclohexylcarbamate

(79a) Compound 76a (20 mg) was dissolved in THF (4 mL)
 25 prior to the addition of saturated NaHCO₃ solution (0.5 mL) and methyl chloroformate (0.5 mL). After 3 h, EtOAc was added along with saturated NaHCO₃ solution. The EtOAc layer was washed with NaHCO₃ solution (aq), dried (MgSO₄), filtered, and concentrated. Reverse phase HPLC
 30 purification (gradient elution, water/acetonitrile/TFA) of the resulting residue provided the title compound (9.3 mg). MS found: (M+ H)⁺ = 582.2.

Example 80

N-((S)-1-((1S,2R,4R)-4-Formamido-2-
(phenylsulfonylmethyl)cyclohexyl)-2-oxopyrrolidin-3-yl)-
3-(trifluoromethyl)benzamide

5

(80a) Compound 76a (30 mg) was dissolved in DMF prior to the addition of 4-methylmorpholine (NMM) (481.5 mg) and concentrated formic acid (0.1 mL). After cooling to 0 °C, EDC (20 mg) was added. The resulting mixture was warmed
 10 to rt and was stirred overnight. EtOAc was added along with saturated NaHCO₃ solution. The EtOAc layer was washed with NaHCO₃ solution (aq), dried (MgSO₄), filtered, and concentrated. Reverse phase HPLC purification (gradient elution, water/acetonitrile/TFA) of the
 15 resulting residue provided the title compound (9.1 mg). MS found: (M+ H)⁺ = 552.3.

Example 81

1-((1R,3R,4S)-4-((S)-2-Oxo-3-(3-
 20 (trifluoromethyl)benzamido)pyrrolidin-1-yl)-3-
(phenylsulfonylmethyl)cyclohexyl)urea

(81a) Compound 76a (77 mg) was dissolved in CH₂Cl₂ (2 mL) at 0 °C prior to the addition of 2,6-lutidine (51 mg) and
 25 phenyl chloroformate (38 mg). After 1 h at rt, CH₂Cl₂ was added along with saturated NaHCO₃ solution. The organic layer was washed with NaHCO₃ solution (aq), dried (MgSO₄), filtered, and concentrated. Flash chromatography of the resulting residue provided phenyl (1R,3R,4S)-4-((S)-2-
 30 oxo-3-(3-(trifluoromethyl)benzamido)pyrrolidin-1-yl)-3-(phenylsulfonylmethyl)cyclohexylcarbamate (43.7 mg). MS found: (M+ H)⁺ = 644.3.

(81b) A portion of the above compound (81a) (20 mg) was dissolved in DMSO (1 mL) prior to the addition of concentrated ammonium hydroxide solution (0.5 mL). After 1 h, the mixture was filtered. The filtrate was purified by reverse phase HPLC purification (gradient elution, water/acetonitrile/TFA) to provide the title compound (4.9 mg). MS found: $(M+H)^+ = 567.3$.

10

Example 82

1-Methyl-3-((1R,3R,4S)-4-((S)-2-oxo-3-(3-(trifluoromethyl)benzamido)pyrrolidin-1-yl)-3-(phenylsulfonylmethyl)cyclohexyl)urea

15 (82a) 2.0 M Methylamine in THF was incorporated into Example 81 to give the title compound. MS found: $(M+H)^+ = 581.3$.

Example 83

20 N-((S)-2-Oxo-1-((1S,2R,4R)-4-(2-oxopyrrolidin-1-yl)-2-(phenylsulfonylmethyl)cyclohexyl)pyrrolidin-3-yl)-3-(trifluoromethyl)benzamide

(83a) 4-Chlorobutyrylchloride (27 mg, 0.191 mmol) was added dropwise to compound 76b (50 mg) and triethylamine (97 mg, 0.722 mmol) in CH_2Cl_2 (2 mL) at room temperature under nitrogen. After 1 h the reaction was diluted with ethyl acetate (12 mL) then washed with water (1 × 5 mL), 10% citric acid (1 × 5 mL), sat'd NaHCO_3 (1 × 5 mL), and brine (1 × 5 mL), dried over MgSO_4 , and evaporated to dryness. The residue was purified by flash chromatography (silica gel, 80% ethyl acetate/hexanes to

10% methanol/ethyl acetate) to provide N-((S)-1-
 ((1S,2R,4R)-4-(4-chlorobutanamido)-2-
 (phenylsulfonylmethyl)cyclohexyl)-2-oxopyrrolidin-3-yl)-
 3-(trifluoromethyl)benzamide as a clear film (40 mg).

5 ESI MS m/z 628 [C₂₉H₃₃ClF₃N₃O₅S + H]⁺.

(83b) The above compound (83a) (40 mg) in THF (1 mL) was
 added to sodium hydride (60% in mineral oil, 5 mg, 0.128
 mmol) in THF (2 mL) at room temperature under nitrogen.
 10 After 3 h the reaction was quenched with sat'd NH₄Cl (5
 mL) and extracted with ethyl acetate (3 × 5 mL). The
 combined organic extracts were washed with brine (1 × 5
 mL), dried over MgSO₄, then evaporated to dryness. The
 residue was purified using C18 HPLC (acetonitrile/water
 15 0.05%TFA) to give the title compound (21.7 mg) as a white
 powder after lyophilization. ESI MS m/z 592 [C₂₉H₃₂F₃N₃O₅S
 + H]⁺.

Example 84

20 N-((S)-1-((1S,2R,4R)-4-(1,1-dioxido-isothiazolidin-2-yl)-
2-(phenylsulfonylmethyl)cyclohexyl)-2-oxopyrrolidin-3-
yl)-3-(trifluoromethyl)benzamide

(84a) 3-Chloropropanesulfonylchloride was incorporated
 25 into Example 83 (in place of 4-chlorobutyrylchloride) to
 give the title compound. MS found: (M + H)⁺ = 628.

Example 85

N-((S)-1-((1S,2R,4R)-2-((4-Chlorophenylsulfonyl)methyl)-
 30 4-(isopropyl(methyl)amino)cyclohexyl)-2-oxopyrrolidin-3-
yl)-3-fluoro-5-(trifluoromethyl)benzamide
trifluoroacetate

(85a) A portion of compound (61g) (500 mg) and 10% Pd/C (112 mg) in MeOH (150 mL) was hydrogenated at 40 psi on a Paar shaker for 4 h. The mixture was filtered through
 5 diatomaceous earth, rinsed with MeOH, then evaporated to dryness to give tert-butyl (1R,3R,4S)-4-amino-3-(hydroxymethyl)cyclohexylcarbamate as a colorless oil (348 mg). ESI MS m/z 245 [$C_{12}H_{24}N_2O_3 + H$]⁺.

10 (85b) To a portion of the above (85a) (4.14 g) in CH₂Cl₂ (169 mL) was added sodium bicarbonate (1.53 g), followed by dropwise addition of TrocCl (2.48 mL). The mixture was stirred at room temperature overnight, then diluted with CH₂Cl₂ (800 mL), washed with satd NaHCO₃ (3 × 150 mL)
 15 and brine (100 mL), dried over Na₂SO₄, filtered, and concentrated to (1S,2R,4R)-(4-tert-butoxycarbonylamino-2-hydroxymethylcyclohexyl)carbamic acid 2,2,2-trichloroethyl ester (7.14 g) as a white solid. ESI MS m/z 319 [$C_{15}H_{25}Cl_3N_2O_5 - Boc + H$]⁺.

20

(85c) A mixture of 85b (7.14 g), bis(*p*-chlorophenyl)disulfide (9.76 g, 34 mmol), and tri-*n*-butylphosphine (26 mL, 187 mmol) in THF (426 mL) was stirred under a nitrogen atmosphere at 75 °C for 16 h.
 25 The solvent was removed under vacuum, the residue was diluted with MeCN (800 mL), washed with hexanes (4 × 200 mL), concentrated, and flash chromatography (silica-gel, 0-50% ether/hexanes) afforded (1R,3R,4S)-[3-(4-chlorophenylsulfanylmethyl)-4-(2,2,2-trichloroethoxycarbonylamino)-cyclohexyl]carbamic acid
 30 tert-butyl ester (6.73 g) as a white solid: ¹H NMR (300 MHz, CDCl₃) δ 7.30-7.18 (m, 4H), 5.06 (d, *J* = 9.2 Hz, 1H), 4.78 (d, *J* = 12.1 Hz, 1H), 4.69 (d, *J* = 12.1 Hz, 1H),

4.46 (d, $J = 7.5$ Hz, 1H), 4.20–4.09 (m, 1H), 3.42 (br s, 1H), 2.94 (dd, $J = 13.4, 7.2$ Hz, 1H), 2.69 (dd, $J = 13.4, 7.2$ Hz, 1H), 2.22–2.08 (m, 1H), 2.05–1.78 (m, 3H), 1.68–1.38 (m, 10H), 1.34–0.82 (m, 2H).

5

(85d) A solution of 85c (6.73 g) in CH_2Cl_2 (41 mL) was cooled to 0 °C; 3-chloroperoxy-benzoic acid (70%, 6.38 g, 25.8 mmol) was added portion-wise. The mixture was stirred for 4 h, then diluted with CH_2Cl_2 (800 mL), washed
10 with satd NaHCO_3 (3 × 150 mL) and brine (100 mL), dried over Na_2SO_4 , filtered, and concentrated to give (1R,3R,4S)-[3-(4-chlorobenzenesulfonylmethyl)-4-(2,2,2-trichloroethoxycarbonylamino) cyclohexyl]carbamic acid tert-butyl ester (7.13 g) as an off-white solid. ESI MS
15 m/z 478 [$\text{C}_{21}\text{H}_{28}\text{Cl}_4\text{N}_2\text{O}_6\text{S} - \text{Boc} + \text{H}$]⁺.

(85e) To a solution of 85d (1.00 g) in THF (16 mL) was added glacial acetic acid (33 mL), followed by activated zinc dust (3.00 g). The mixture was stirred for 8 h,
20 then diluted with EtOAc (500 mL), washed with satd Na_2CO_3 (3 × 150 mL) and brine (100 mL), dried over Na_2SO_4 , filtered, and concentrated. The residue was purified by CombiFlash chromatography (silica-gel, $\text{MeOH}/\text{CH}_2\text{Cl}_2$) to give tert-butyl (1R,3R,4S)-4-amino-3-((4-
25 chlorophenylsulfonyl)methyl)cyclohexylcarbamate (561 mg) as yellow solid. ESI MS m/z 403 [$\text{C}_{18}\text{H}_{27}\text{ClN}_2\text{O}_4\text{S} + \text{H}$]⁺.

(85f) To a solution of 85e (561 mg) and *N*-Cbz-L-methionine (591 mg) in DMF (9.3 mL), cooled to 0 °C, was
30 added *N*-methylemorpholine (458 μL) and BOP reagent (925 mg). The mixture was stirred overnight at room temperature, then diluted with EtOAc (500 mL), washed with satd NaHCO_3 (3 × 150 mL), NH_4Cl (3 × 150 mL), 5%

aqueous LiCl (3 × 150 mL), and brine (100 mL), dried over Na₂SO₄, filtered, and concentrated to give crude (1R,3R,4S)-[4-(2-benzyloxycarbonylamino-4-methylsulfanylbutyrylamino)-3-(4-chlorobenzenesulfonylmethyl)cyclohexyl]carbamic acid tert-butyl ester (953 mg) as a yellow solid. ESI MS *m/z* 668 [C₃₁H₄₂ClN₃O₇S₂ + H]⁺.

(85g) A mixture of 85f (6.42 g, 9.60 mmol) and iodomethane (70 mL) was stirred overnight at room temperature. Methylene chloride (200 mL) was added and the iodomethane was azeotroped off under vacuum, repeating 6-8 times. The residue was dissolved in CH₂Cl₂ (200 mL), concentrated to ¼ volume under vacuum, and the resultant white solid was filtered (2.47 g, sulfonium salt by-product). The filtrate was concentrated to provide a yellow solid (6.80 g), which was used without further purification. This yellow solid (6.80 g), cesium carbonate (5.47 g, 16.8 mmol), and DMF (129 mL) was stirred 6 h at room temperature. More cesium carbonate (5.47 g, 16.8 mmol) was added and the reaction was stirred overnight. The mixture was diluted with EtOAc (1 L), washed with water (3 × 600 mL), 5% aqueous LiCl (3 × 600 mL), and brine (450 mL), dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography (silica-gel, 50-100% EtOAc/hexanes) to give (1S,2R,4R)-{1-[4-tert-butoxycarbonylamino-2-(4-chlorobenzenesulfonylmethyl) cyclohexyl]-2-oxo-pyrrolidin-3-yl}carbamic acid benzyl ester (3.21 g) as white solid. ESI MS *m/z* 620 [C₃₀H₃₈ClIN₃O₇S + H]⁺.

(85h) Compound 85g was incorporated into step 62b to give benzyl (S)-1-((1S,2R,4R)-4-amino-2-((4-

chlorophenylsulfonyl)methyl)cyclohexyl)-2-oxopyrrolidin-3-ylcarbamate: ^1H NMR (300 MHz, CDCl_3) δ 10.46 (br, s, 3H), 7.90–7.60 (m, 4H), 7.55–7.42 (m, 2H), 7.40–7.29 (m, 3H), 5.65 (d, J = 7.3 Hz, 1H), 4.88 (s, 2H), 4.34–4.09 (m, 2H), 3.86–3.64 (m, 1H), 3.60–3.20 (m, 4H), 2.77–2.30 (m, 3H), 2.20–1.70 (m, 6H).

(85i) A mixture of 85h (875 mg, 1.38 mmol), acetone (3.03 mL, 41.4 mmol), and acetic acid (159 μL , 2.76 mmol) in 1,2-dichloroethane (30 mL) was stirred for 3 min, then treated with sodium triacetoxymethylborohydride (585 mg, 2.76 mmol). After stirring the mixture for 3 h, more acetone (4 mL), acetic acid (0.4 mL), and sodium triacetoxymethylborohydride (300 mg, 1.42 mmol) were added. After stirring the reaction mixture overnight, the solvent was removed under vacuum. The residue was dissolved in MeOH (30 mL); 37% aqueous formaldehyde (6 mL) and sodium cyanoborohydride (130 mg, 2.07 mmol) were added. The mixture was stirred 8 h. The solvent was removed under vacuum; the residue was taken up in CH_2Cl_2 (300 mL), washed with satd NaHCO_3 (3 \times 100 mL) and brine (100 mL), dried over Na_2SO_4 , filtered, and concentrated under vacuum to afford benzyl (S)-1-((1S,2R,4R)-2-((4-chlorophenylsulfonyl)methyl)-4-(isopropyl(methyl)amino)cyclohexyl)-2-oxopyrrolidin-3-ylcarbamate (707 mg) as a yellow solid. ESI MS m/z 576 $[\text{C}_{29}\text{H}_{38}\text{ClN}_3\text{O}_5\text{S} + \text{H}]^+$.

(85j) A mixture of 85i (536 mg) and 33% HBr in HOAc (15 mL) was stirred 30 minutes at room temperature. The mixture was triturated with ether (3 \times 50 mL) and the residue was dissolved in MeOH (50 mL). The solvent was evaporated under vacuum to provide (S)-3-amino-1-

((1S,2R,4R)-2-((4-chlorophenylsulfonyl)methyl)-4-(isopropyl(methyl)amino)cyclohexyl)pyrrolidin-2-one dihydrogen bromide (436 mg) as a tan solid, which was used without further purification in the next step. ESI
 5 MS m/z 442 [$C_{21}H_{32}ClN_3O_3S + H$]⁺.

(85k) To a solution of crude 85j (92 mg) and 3-fluoro-5-(trifluoromethyl)benzoic acid (48 mg) in DMF (1.01 mL), cooled to 0 °C, was added *N*-methyilmorpholine (50 µL) and
 10 BOP reagent (101 mg). The mixture was stirred overnight at room temperature, diluted with EtOAc (500 mL), washed with satd NaHCO₃ (3 × 150 mL), NH₄Cl (3 × 150 mL), 5% aqueous LiCl (3 × 150 mL), and brine (100 mL), dried over Na₂SO₄, filtered, and concentrated. The residue was
 15 purified by semi-preparative HPLC to give the title compound (71.2 mg) as a •TFA salt after lyophilization from MeCN/H₂O. ESI MS m/z 632 [$C_{29}H_{34}ClF_4N_3O_4S + H$]⁺.

Example 86

20 3-Chloro-N-((S)-1-((1S,2R,4R)-2-((4-chlorophenylsulfonyl)methyl)-4-(isopropyl(methyl)amino)cyclohexyl)-2-oxopyrrolidin-3-yl)benzamide trifluoroacetate

25 (86a) 3-Chlorobenzoic acid was incorporated into Example 85 (step 85k) to give the title compound. MS found: (M + H)⁺ = 580.

Example 87

30 N-((S)-1-((1S,2R,4R)-2-((4-chlorophenylsulfonyl)methyl)-4-(isopropyl(methyl)amino)cyclohexyl)-2-oxopyrrolidin-3-yl)-3,5-bis(trifluoromethyl)benzamide trifluoroacetate

(87a) 3,5-Bis(trifluoromethyl)benzoic acid was incorporated into Example 85 (step 85k) to give the title compound. MS found: $(M + H)^+ = 683$.

5

Example 88

tert-Butyl 2-(((S)-1-((1S,2R,4R)-2-((4-chlorophenylsulfonyl)methyl)-4-(isopropyl(methyl)amino)cyclohexyl)-2-oxopyrrolidin-3-yl)carbamoyl)-4-(trifluoromethoxy)phenylcarbamate

10

(88a) 2-tert-Butoxycarbonylamino-5-trifluoromethoxybenzoic acid was incorporated into Example 85 (step 85k) to give the title compound. MS found: $(M + H)^+ = 746$.

15

Example 89

2-Amino-N-(((S)-1-((1S,2R,4R)-2-((4-chlorophenylsulfonyl)methyl)-4-(isopropyl(methyl)amino)cyclohexyl)-2-oxopyrrolidin-3-yl)-5-(trifluoromethoxy)benzamide trifluoroacetate

20

(89a) Example 88 was incorporated into Example 62 (step 62b) to give the title compound. MS found: $(M + H)^+ = 645$.

25

Example 90

N-(((S)-1-((1S,2R,4R)-2-((4-Chlorophenylsulfonyl)methyl)-4-(isopropyl(methyl)amino)cyclohexyl)-2-oxopyrrolidin-3-yl)-3-(trifluoromethoxy)benzamide trifluoroacetate

30

(90a) 3-Trifluoromethoxybenzoic acid was incorporated into Example 85 (step 85k) to give the title compound. MS found: $(M + H)^+ = 630.2$.

5

Example 91

N-((S)-1-((1S,2R,4R)-2-((4-Chlorophenylsulfonyl)methyl)-4-(isopropyl(methyl)amino)cyclohexyl)-2-oxopyrrolidin-3-yl)-3-(trifluoromethyl)benzamide trifluoroacetate

10 (91a) 3-Trifluoromethylbenzoic acid was incorporated into Example 85 (step 85k) to give the title compound. MS found: $(M + H)^+ = 614.0$.

Example 92

15 3,5-Dichloro-N-((S)-1-((1S,2R,4R)-2-((4-chlorophenylsulfonyl)methyl)-4-(isopropyl(methyl)amino)cyclohexyl)-2-oxopyrrolidin-3-yl)benzamide trifluoroacetate

20 (92a) 3,5-Dichlorobenzoic acid was incorporated into Example 85 (step 85k) to give the title compound. MS found: $(M + H)^+ = 614.2$.

Example 93

25 3-Chloro-N-((S)-1-((1S,2R,4R)-2-((4-chlorophenylsulfonyl)methyl)-4-(isopropyl(methyl)amino)cyclohexyl)-2-oxopyrrolidin-3-yl)benzamide N-Oxide

30 (93a) A solution of Example 86 (13.6 mg) in CH_2Cl_2 (1.5 mL) was cooled to 0 °C, then 3-chloroperoxybenzoic acid

(77%, 10 mg) was added portion-wise. The mixture was stirred for 1.25 h, then diluted with CH₂Cl₂ (400 mL), washed with satd NaHCO₃ (3 × 100 mL) and brine (100 mL), dried over Na₂SO₄, filtered, and concentrated. The
 5 residue was purified by semi-preparative HPLC to give the title compound (6.8 mg, 57%) as a white solid after lyophilization from MeCN/aqueous TFA. ESI MS *m/z* 596 [C₂₈H₃₅Cl₂N₃O₅S + H]⁺.

10

Example 94

N-((S)-1-((1S,2R,4R)-2-((4-Chlorophenylsulfonyl)methyl)-4-(isopropyl(methyl)amino)cyclohexyl)-2-oxopyrrolidin-3-yl)-3-(trifluoromethyl)benzamide N-Oxide

15 (94a) Example 91 was incorporated into Example 93 to give the title compound. MS found: (M + H)⁺ = 630.3.

Example 95

20 N-((S)-1-((1S,2R,4R)-2-((4-Chlorophenylsulfonyl)methyl)-4-(isopropyl(methyl)amino)cyclohexyl)-2-oxopyrrolidin-3-yl)-3-fluoro-5-(trifluoromethyl)benzamide N-Oxide

(95a) Example 85 was incorporated into Example 93 to give the title compound. MS found: (M + H)⁺ = 649.1.

25

Example 96

N-((S)-1-((1S,2R,4R)-4-(Isopropyl(methyl)amino)-2-(phenylsulfonylmethyl)cyclohexyl)-2-oxopyrrolidin-3-yl)-3-(trifluoromethyl)benzamide N-Oxide

30

(96a) Example 5 was incorporated into Example 93 to give the title compound. MS found: $(M + H)^+ = 596.3$.

Example 97

5 N-((S)-1-((1S,2R,4R)-4-(isopropyl(methyl)amino)-2-((4-
isopropylphenylsulfonyl)methyl)cyclohexyl)-2-
oxopyrrolidin-3-yl)-3-(trifluoromethyl)benzamide
 Trifluoroacetate

10 (97a) The compound from step 61f (4.0 g) was dissolved in
MeOH (30 mL) prior to the addition of 10% Pd/C (600 mg).
A hydrogen balloon was added and the mixture was stirred
for 3 h. The Pd/C was filtered off and the solvent was
concentrated to give (1R,2S,5R)-tert-butyl 2-amino-7-oxo-
15 6-aza-bicyclo[3.2.1]octane-6-carboxylate (2.5 g). MS
found: (M + H)⁺ = 241.1.

(97b) This material (97a) was incorporated into Steps 52a to 52b (substituting N-Cbz-L-Met-OH for N-Boc-L-Met-OH) to give (1R,2S,5R)-tert-butyl 2-((S)-3-(benzyloxycarbonyl)-2-oxopyrrolidin-1-yl)-7-oxo-6-azabicyclo[3.2.1]octane-6-carboxylate. MS found: (M + H)⁺ = 458.3.

25 (97c) A mixture of 97b (1.20 g) and 10% Pd/C (558 mg) in MeOH (200 mL) was hydrogenated at 1 atm for 4 h. The mixture was filtered through diatomaceous earth with MeOH wash and evaporated to dryness to give (1R,2S,5R)-tert-butyl 2-((S)-3-amino-2-oxopyrrolidin-1-yl)-7-oxo-6-azabicyclo[3.2.1]octane-6-carboxylate (779 mg) as a yellow solid that was used without further purification in the next step: ¹H NMR (300 MHz, CDCl₃) δ 4.40-4.15 (m, 2H),

3.68 (t, J = 9.0 Hz, 1H), 3.53–3.40 (m, 2H), 3.28–3.12 (m, 1H), 2.70–2.60 (m, 1H), 2.46–2.10 (m, 6H), 1.96–1.60 (m, 5H), 1.54 (s, 9H).

- 5 (97d) To a mixture of 97c (779 mg), 3-(trifluoromethyl)benzoic acid (687 mg), and DMF (12 mL), cooled to 0 °C, was added *N*-methylmorpholine (793 μ L, 7.23 mmol) and BOP reagent (1.60 g, 3.61 mmol). The mixture was stirred overnight at room temperature, diluted with
- 10 EtOAc (800 mL), washed with satd NaHCO₃ (3 \times 150 mL), NH₄Cl (3 \times 150 mL), 5% aqueous LiCl (3 \times 150 mL), and brine (100 mL), dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 0–15% MeOH/CH₂Cl₂) to give
- 15 (1R,2S,5R)-tert-butyl 7-oxo-2-((S)-2-oxo-3-(3-(trifluoromethyl)benzamido)pyrrolidin-1-yl)-6-azabicyclo[3.2.1]octane-6-carboxylate (1.20 g) as white solid. ESI MS m/z 496 [C₂₄H₂₈F₃N₃O₅S + H]⁺.
- 20 (97e) To a solution of 97d (1.20 g, 2.42 mmol) in THF (18.6 mL) and water (3.6 mL) was added sodium borohydride (460 mg, 12.1 mmol) portion wise. After stirring the mixture for three hours, satd NaHCO₃ (50 mL) was added and the mixture was stirred for an additional 15 min. The
- 25 mixture was diluted with ethyl acetate (500 mL), washed with satd NaHCO₃ (3 \times 150 mL) and brine (100 mL), dried over Na₂SO₄, filtered, and concentrated to give tert-butyl (1R,3R,4S)-3-(hydroxymethyl)-4-((S)-2-oxo-3-(3-(trifluoromethyl)benzamido)pyrrolidin-1-
- 30 yl)cyclohexylcarbamate (1.12 g) as a white solid. ESI MS m/z 500 [C₂₄H₃₂F₃N₃O₅ + H]⁺.

(97f) A mixture of 97e (100 mg), bis(*p*-1,2-bis(4-isopropylphenyl)disulfane (121 mg), and tri-*n*-butylphosphine (0.3 mL) in THF (5 mL) was stirred under a nitrogen atmosphere at 75 °C for 16 h. The solvent was removed under vacuum, the residue was diluted with MeCN (500 mL), washed with hexanes (4 × 200 mL), concentrated, and preparative TLC afforded tert-butyl (1*R*,3*R*,4*S*)-3-((4-isopropylphenylthio)methyl)-4-((*S*)-2-oxo-3-(3-(trifluoromethyl)benzamido)pyrrolidin-1-yl)cyclohexylcarbamate (79.7 mg) as a mixture of isomers. ESI MS *m/z* 634 [C₂₄H₃₂F₃N₃O₅ + H]⁺.

(97g) The compound from above (97f) was incorporated into Step 3e to give tert-butyl (1*R*,3*R*,4*S*)-3-((4-isopropylphenylsulfonyl)methyl)-4-((*S*)-2-oxo-3-(3-(trifluoromethyl)benzamido)pyrrolidin-1-yl)cyclohexylcarbamate: ¹H NMR (300 MHz, CDCl₃) δ 8.10–7.76 (m, 4H), 7.75–7.62 (m, 1H), 7.61–7.30 (m, 3H), 4.90–4.04 (m, 2H), 3.87–3.20 (m, 4H), 3.13–2.86 (m, 1H), 2.80–2.42 (m, 1H), 2.36–1.50 (m, 25H), 0.99–0.75 (m, 4H); ¹⁹F NMR (282 MHz, CDCl₃) δ –63.1, –63.2.

(97h) The compound from above (97g) was incorporated into Step 611 to give the title compound after HPLC. MS found: (M + H)⁺ = 622.3.

Example 98

N-((*S*)-1-((1*S*,2*R*,4*R*)-4-(isopropyl(methyl)amino)-2-(*o*-tolylsulfonylmethyl)cyclohexyl)-2-oxopyrrolidin-3-yl)-3-(trifluoromethyl)benzamide trifluoroacetate

(98a) 1,2-diortho-tolyldisulfane was incorporated into Example 97 from Step 97f to 97h to give the title compound. MS found: $(M + H)^+ = 594.6$.

5

Example 99

N-((S)-1-((1S,2R,4R)-2-((4-Fluorophenylsulfonyl)methyl)-4-(isopropyl(methyl)amino)cyclohexyl)-2-oxopyrrolidin-3-yl)-3-(trifluoromethyl)benzamide trifluoroacetate

10 (99a) 1,2-bis(4-Fluorophenyl)disulfane was incorporated into Example 97 from Step 97f to 97h to give the title compound. MS found: $(M + H)^+ = 598.5$.

Example 100

15 3-Chloro-N-((S)-1-((1S,2R,4R)-4-(isopropyl(methyl)amino)-2-(tosylmethyl)cyclohexyl)-2-oxopyrrolidin-3-yl)benzamide trifluoroacetate

(100a) Compound 97b was incorporated into Step 97e to
20 give (1S,2R,4R)-{1-[4-tert-butoxycarbonylamino-2-(hydroxymethyl)cyclohexyl]-2-oxo-pyrrolidin-3-yl}carbamic acid benzyl ester. MS found: $(M + H)^+ = 462$.

(100b) Compound 100a was incorporated into Step 97f (with
25 1,2-dipara-tolyldisulfane instead of bis(p-1,2-bis(4-isopropylphenyl)disulfane) and then Step 97g to give (1S,2R,4R)-{1-[4-tert-butoxycarbonylamino-2-(4-methylbenzenesulfonylmethyl)cyclohexyl]-2-oxo-pyrrolidin-3-yl}carbamic acid benzyl ester. MS found: (M
30 + H)⁺ = 600.

(100c) Compound 100b was taken into Steps 85h-85j to give
 (S)-3-amino-1-((1S,2R,4R)-2-((4-
 methylphenylsulfonyl)methyl)-4-
 (isopropyl(methyl)amino)cyclohexyl)pyrrolidin-2-one
 5 dihydrogen bromide. MS found: $(M + H)^+ = 584$.

(100d) Compound 100c was taken into Step 85k (with 3-
 chlorobenzoic acid instead 3-fluoro-5-trifluoromethyl-
 benzoic acid) to give the title compound. MS found: $(M +$
 10 $H)^+ = 560.2$.

Example 101

2-Amino-N-((S)-1-((1S,2R,4R)-4-(isopropyl(methyl)amino)-
2-(tosylmethyl)cyclohexyl)-2-oxopyrrolidin-3-yl)-5-
 15 (trifluoromethoxy)benzamidide trifluoroacetate

(101a) 2-(tert-Butoxycarbonyl)-5-(trifluoromethyl)benzoic
 acid was incorporated into Step, (100d) to give tert-butyl
 2-(((S)-1-((1S,2R,4R)-4-(isopropyl(methyl)amino)-2-
 20 (tosylmethyl)cyclohexyl)-2-oxopyrrolidin-3-yl)carbonyl)-
 4-(trifluoromethoxy)phenylcarbamate. MS found: $(M + H)^+ =$
 725.

(101b) The above material (101a) (20 mg) was dissolved in
 25 CH_2Cl_2 (2 mL) and cooled to 0 °C prior to the addition of
 TFA (4 mL). After the reaction was warmed to rt over 30
 min, it was concentrated and dried to provide the title
 compound. MS found: $(M + H)^+ = 625.2$.

Example 102

1-[(1S, 2R, 4R)-(4-Amino-2-benzenesulfonyl-methylcyclohexyl)-4-(3-trifluoromethylphenyl)]-5,6-dihydro-1H-pyridin-2-one

5

(102a) A solution of compound 61j (1.45 g, 3.9 mmol) in methanol (10 mL) was stirred on an ice bath and treated dropwise over 40 min with a solution of 1-(3-trifluoromethylphenyl)propenone (see procedure 28a, 786 mg, 3.9 mmol). The mixture was stirred at room temperature for 2 h, then was concentrated under vacuum. The residue was purified by flash column chromatography, eluting with 55% ethyl acetate-hexane, to provide (1R,3R,4S)-{3-benzene-sulfonylmethyl-4-[3-oxo-3-(3-trifluoromethylphenyl)-propylamino]cyclohexyl}carbamic acid tert-butyl ester (1.16 g) as a white glassy solid. MS found: (M + H)⁺ = 569.35.

(102b) A suspension of sodium hydride (60%, 176 mg, 4.4 mmol) in tetrahydrofuran (5 mL) was stirred on an ice bath and treated dropwise over 5 min with dimethylphosphonoacetic acid tert-butyl ester (0.79 mL, 4.0 mmol). The mixture was stirred at room temperature for 25 min, then was cooled on an ice bath and treated with a solution of (1R,3R,4S)-{3-benzenesulfonylmethyl-4-[3-oxo-3-(3-trifluoromethylphenyl)-propylamino]cyclohexyl}carbamic acid tert-butyl ester (1.138 g, 2.0 mmol) in tetrahydrofuran (5 mL). The mixture was stirred at room temperature for 2.5 h, then was treated with saturated aqueous ammonium chloride. The mixture was extracted with ethyl acetate, and the organic extracts were dried over sodium sulfate and concentrated under vacuum. The residue was purified by flash column chromatography, eluting with 25% ethyl acetate-hexane, to provide the E isomer of 5-([1S,2R,4R]-2-benzenesulfonylmethyl-4-tert-butoxycarbonyl-aminocyclohexylamino)-3-(3-trifluoromethylphenyl)pent-2-

enoic acid tert-butyl ester (511 mg) as a white solid. MS found: $(M + H)^+ = 667.41$. Further elution with 40% ethyl acetate-hexane provided the corresponding Z isomer (567 mg) as a white glassy solid. MS found: $(M + H)^+ = 667.41$.

5

(102c) A solution of the E isomer of 5-([1S,2R,4R]-2-benzenesulfonylmethyl-4-tert-butoxycarbonylaminocyclohexyl-amino)-3-(3-trifluoromethylphenyl)pent-2-enoic acid tert-butyl ester (495 mg) in dichloromethane (10 mL) was treated with trifluoroacetic acid (5 mL). After standing at room temperature for 4 h, the mixture was concentrated under vacuum to provide the E isomer of 5-([1S,2R,4R]-4-amino-2-benzenesulfonylmethylcyclohexylamino)-3-(3-trifluoromethyl-phenyl)pent-2-enoic acid, bis-trifluoroacetic acid salt, as a white glassy solid (736 mg) containing excess trifluoro-acetic acid. MS found: $(M + H)^+ = 511.20$. Without further purification, this material was dissolved in dichloromethane (5 mL) and treated sequentially with diisopropylethylamine (0.78 mL, 4.45 mmol), 4-(N,N-dimethylamino)pyridine (91 mg, 0.74 mmol) and TBTU (262 mg, 0.82 mmol). The solution was stirred at room temperature for 17.5 h, then was diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate, dried over sodium sulfate and concentrated under vacuum. The residue was purified by flash column chromatography, eluting with 4% methanol-dichloromethane containing 0.4% aqueous ammonia, and then by reverse phase HPLC. The resulting product was converted to the free base by partitioning between 1N sodium hydroxide and ethyl acetate to provide the title product (130 mg) as a white glassy foam. MS found: $(M + H)^+ = 493.37$.

35

Example 103

1-([(1*S*, 2*R*, 4*R*)-2-benzenesulfonylmethyl-4-isopropylamino-cyclohexyl]-4-(3-trifluoromethylphenyl)-5,6-dihydro-1*H*-pyridin-2-one

5 (103a) A solution of 1-([(1*S*, 2*R*, 4*R*)-(4-amino-2-benzenesulfonyl-methylcyclohexyl)-4-(3-trifluoromethylphenyl)]-5,6-dihydro-1*H*-pyridin-2-one (120 mg, 0.243 mmol) in 1,2-dichloroethane (2.5 mL) was treated sequentially with acetone (0.054 mL, 0.071 mmol),
 10 acetic acid (0.07 mL, 1.22 mmol) and sodium triacetoxyborohydride (155 mg, 0.731 mmol). The mixture was stirred at room temperature for 3 h, then was concentrated under vacuum. The residue was partitioned between saturated aqueous sodium bicarbonate and ethyl
 15 acetate, and the organic extracts were dried over sodium sulfate and concentrated under vacuum to provide the title product (110 mg) as a white glassy solid. MS found: (M + H)⁺ = 535.21.

20 **Example 104**

1-[(1*S*, 2*R*, 4*R*)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)cyclohexyl]-4-(3-trifluoromethyl-phenyl)-5,6-dihydro-1*H*-pyridin-2-one

25 (104a) A solution of 1-([(1*S*, 2*R*, 4*R*)-2-benzenesulfonylmethyl-4-isopropylamino-cyclohexyl)-4-(3-trifluoromethylphenyl)-5,6-dihydro-1*H*-pyridin-2-one (41 mg, 0.077 mmol) in methanol (1 mL) was treated with aqueous formaldehyde (37%, 0.029 mL, 0.383 mmol) and the
 30 mixture was stirred for 45 min. Sodium cyanoborohydride (7 mg, 0.115 mmol) was added, and the mixture stirred at room temperature for 2 h. Water was added and the mixture was extracted with ethyl acetate. The extracts were washed with brine, dried over sodium sulfate and
 35 concentrated under vacuum to provide the title product (42 mg) as a white glassy solid. MS found: (M + H)⁺ = 548.67.

Example 105

1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-ethyl-amino)cyclohexyl]-4-(3-trifluoromethyl-phenyl)-5,6-
dihydro-1H-pyridin-2-one

(105a) Following the procedure of Example 104 but substituting acetaldehyde for aqueous formaldehyde, 1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-isopropylamino-cyclohexyl]-4-(3-trifluoromethylphenyl)-5,6-dihydro-1H-pyridin-2-one (43 mg, 0.08 mmol) was converted to the title product (45 mg) as a white glassy solid. MS found: (M + H)⁺ = 563.29.

Example 106

1-[(1S, 2R, 4R)-2-Benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-(3S)-3-(6-chloro-2-trifluoromethyl-quinazolin-4-ylamino)-pyrrolidin-2-one,
TFA salt

Part A. Preparation of 6-Chloro-2-trifluoromethyl-quinazolin-4-ol

2-Amino-5-chlorobenzamide (Avocado) (1.00 g, 5.86 mmol, 1.0 eq.) and ethyl trifluoroacetate (4.19 mL, 35.2 mmol, 6.0 eq.) were dissolved in 50 mL of ethanol at rt under nitrogen and followed by the addition of 3.09 M sodium ethoxide in ethanol (11.38 mL, 35.2 mmol, 6.0 eq.) The mixture was refluxed 20 hours. Cooled to rt. Added 10 mL of 10% HOAc/H₂O. Solids formed which were filtered, rinsed with 5 mL H₂O, then dissolved in 20 mL of EtOAc/THF. Dried and stripped in vacuo to give 1.35 g of amber solids. LCMS detects (M+H)⁺ = 249.

Part B. Preparation of 4,6-Dichloro-2-trifluoromethyl
quinazoline

6-Chloro-2-trifluoromethyl-quinazolin-4-ol (1.35 g, 5.43
5 mmol, 1 eq.), phosphorous oxychloride (4.88 mL, 52.4
mmol, 9.64 eq.) and triethylamine (2.43 mL, 17.4 mmol,
3.21 eq.) were refluxed for 2 hours. Stripped 3X from
methylene chloride then dissolved in methylene chloride
and rinsed 3X with saturated sodium bicarbonate, 1X with
10 brine. Dried and stripped in vacuo to give an amber oil.
Purified over silica gel in 9:1 Hexanes/EtOAc. Obtained
800 mg of off-white solids as product. The product was
used immediately in Example 1 Part C.

15 Part C.

(3S)-3-Amino-1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-
(isopropyl-methyl-amino)-cyclohexyl]-pyrrolidin-2-one (40
mg, 0.0982 mmol, 1 eq., see compound 52e), 4,6-dichloro-
20 2-trifluoromethyl-quinazoline (239 mg, 0.105 mmol, 1 eq.)
and triethylamine (55 ul, 0.419, 4 eq.) were dissolved
in 3 mL of ethanol then microwaved at 100 °C until
reaction was complete by LCMS. Purified by LCMS.
Obtained 17 mg of product. LCMS detects (M+H)+ = 638.

25

Example 107

1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-
methyl-amino)-cyclohexyl]-(3S)-3-(7-chloro-quinazolin-4-
ylamino)-pyrrolidin-2-one, TFA salt

30

Part A. Preparation of 7-Chloro-quinazolin-4-ol

2-Amino-4-chloro-benzoic acid (1.00 g, 11.7 mmol, 1.0 eq.), formamidine acetate (3.64 mL, 35.0 mmol, 3 eq.), and ethoxyethanol (20 mL) were refluxed under nitrogen overnight. Cooled to rt. Added 25 mL of diethyl ether.
5 Solids precipitated. Filtered off solids. Pumped under high vacuum to give 2.75 g of white solids as product. LCMS detects (M+H)+ = 181.

Part B. Preparation of 4,7-Dichloro-quinazoline

10 7-Chloro-quinazolin-4-ol (1.1 g, 6.09 mmol, 1 eq.), phosphorous oxychloride (5.47 mL, 58.7 mmol, 9.00 eq.) and triethylamine (2.73 mL, 19.6 mmol, 3.21 eq.) were refluxed for 2 hours. Stripped then restripped 3X from
15 methylene chloride, then dissolved in methylene chloride and rinsed 3X with saturated sodium bicarbonate, 1X with brine. Dried and stripped in vacuo to give an amber oil. Purified over silica gel in 9:1 to 3:1 Hexanes/EtOAc. Obtained 1.00 g of tan solids as product. LCMS detects
20 (M+H)+ = 199.

107. Part C. Preparation of 1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-(3S)-3-(7-chloro-quinazolin-4-ylamino)-pyrrolidin-2-one, TFA salt
25

Followed the procedure of Example 106c starting from (3S*)-3-amino-1-[(1S*, 2R*, 4R*)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-pyrrolidin-2-one and
30 4,7-dichloro-quinazoline. LCMS detects (M+H)+ = 570.

Example 108

Part A Preparation of 6-Chloro-quinazoline-2,4-diol

2-Amino-5-chlorobenzamide (Avocado) (3.00 g, 17.5 mmol, 1.0 eq.) was suspended in 105 mL of H₂O and 1.75 mL of
5 HOAc at rt. A 12 mL solution of H₂O and sodium cyanate (2.80 g, 43.0 mmol, 2.46 eq.) was then added slowly. Stirred at 35 °C for 1 hour. Added 31.26 mL of 1.0 N NaOH slowly. Solids precipitated. Cooled to 0°C. Carefully added conc. HCl to pH = 3. Filtered solids. Solids were
10 then stirred in diethyl ether then refiltered and pumped under high vacuum to give 3.36 grams of tan solids as product. LCMS detects (M+H)+ = 197.

Part B. Preparation of 2,4,6-Trichloro-quinazoline

15 6-Chloro-quinazoline-2,4-diol (0.50 g, 2.54 mmol, 1 eq.), phosphorous oxychloride (2.14 mL, 22.9 mmol, 9 eq.) and 2,6-lutidine (0.44 mL, 3.82 mmol, 1.5 eq.) were refluxed under nitrogen for 2 hours. The reaction was stripped then restripped 3X from methylene chloride, then
20 dissolved in methylene chloride and rinsed 3X with saturated sodium bicarbonate, 1X with brine. Dried and stripped in vacuo to give an amber oil. Purified over silica gel in 9:1 to 3:1 Hexanes/EtOAc. Obtained 0.22 g of light colored solids as product. ¹H NMR (400 MHz)
25 (CD₃OD) δ 8.36 (s, 1H), 8.09 (d, 1H, J = 7 Hz), 7.97 (d, 1H, J = 7 Hz).

Example 108. Part C. Preparation of 1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-(3S)-3-(2,6-dichloro-quinazolin-4-ylamino)-pyrrolidin-2-one, TFA salt

5

(3S)-3-Amino-1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-pyrrolidin-2-one (75 mg, 0.184 mmol, 1 eq.), 2,4,6-trichloro-quinazoline (43 mg, 0.184 mmol, 1 eq.) N,N-diisopropylethylamine (64 mL, 0.368 mmol, 2 eq.) in THF (3 mL) were refluxed overnight. Purified by HPLC. Obtained 62 mg of white solids. LCMS detects (M+H)+ = 604.

10

Example 109

Preparation of 1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-(3S)-3-(6-chloro-2-dimethylamino-quinazolin-4-ylamino)-pyrrolidin-2-one, TFA salt

1-[(1S*, 2R*, 4R*)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-(3S*)-3-(2,6-dichloro-quinazolin-4-ylamino)-pyrrolidin-2-one (27 mg, 0.0375 mmol, 1 eq.), 2.0 M dimethylamine in THF (0.94 mL, 1.88 mmol, 50 eq.), and THF (1 mL) were refluxed until reaction was complete by LCMS. Purified by HPLC. Obtained 22 mg of white solids as product. LCMS detects (M+H)+ = 613.

20

25

30

Example 110

Preparation of 1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-(3S)-3-(6-chloro-2-hydroxy-quinazolin-4-ylamino)-pyrrolidin-2-one, TFA salt

1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-(3S)-3-(2,6-dichloro-quinazolin-4-ylamino)-pyrrolidin-2-one (20 mg) and
5 dimethyl sulfoxide (2 mL) were heated at 60 °C under nitrogen until reaction was complete by LCMS. Purified by HPLC to give 6.0 mg of white solids as product. LCMS detects (M+H)+ = 586.

10

Example 111**Part A. Preparation of 6-Trifluoromethyl-quinazolin-4-ol**

2-Amino-5-trifluoromethyl-benzamide (ButtPark) (1.00 g, 4.90 mmol, 1 eq.) and formic acid (3.30 mL, 87.2 mmol, 17.8 eq.) were refluxed for 2.5 hours. Cooled to rt then
15 added water (10 mL). Stirred 15 minutes then filtered off solids which were present. The solids were dried at 110 °C for 3 hours to give 520 mg of white solids as product. LCMS detects (M+H)+ = 215.

20

Part B. Preparation of 4-Chloro-6-trifluoromethyl-quinazoline

6-Trifluoromethyl-quinazolin-4-ol (0.95 g, 4.44 mmol, 1 eq.), phosphorous oxychloride (2.48 mL, 26.6 mmol, 6 eq.) and triethylamine (3.71 mL, 26.6 mmol, 6 eq.) were
25 refluxed for 2.5 hours. Stripped 3X from methylene chloride then dissolved in methylene chloride and rinsed 3X with saturated NaHCO₃, 1X with brine. Dried and
30 stripped in vacuo to give an amber oil. Purified over silica gel in 9:1 Hexanes/EtOAc. Obtained 560 mg of off-

white solids as product. The product was used immediately in Ex 111 part C.

Example 111 Part C. Preparation of 1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-(3S)-3-(6-trifluoromethyl-quinazolin-4-ylamino)-pyrrolidin-2-one, TFA salt

Followed the procedure of Example 106 Part C starting from (3S)-3-amino-1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-pyrrolidin-2-one and 4-Chloro-6-trifluoromethyl-quinazoline. Purified by HPLC. Obtained 57 mg of white solids as title product. LCMS detects (M+H)⁺ = 604.

Example 112

Part A. Preparation of 6-tert-Butyl-thieno[3,2-d]pyrimidin-4-ol

3-Amino-5-tert-butyl-thiophene-2-carboxylic acid methyl ester (1.00 g, 4.69 mmol, 1 eq.), formamidine acetate (1.46 g, 4.69 mmol, 3 eq.) and 2-ethoxyethanol (10 mL) were refluxed under nitrogen for 4 hours. Purified over silica gel in 3:1 to 1:1 Hexanes/ethyl acetate to 100% ethyl acetate to obtain 970 mg of yellow solids as product. LCMS detects (M+H)⁺ = 209.

30

Part B. Preparation of 6-tert-Butyl-4-chloro-thieno[3,2-d]pyrimidine

6-tert-Butyl-thieno[3,2-d]pyrimidin-4-ol (500 mg, 2.40 mmol, 1 eq.) and phosphorous oxychloride (4.48 mL, 48.0 mmol, 20 eq.) were refluxed under nitrogen for 1.5 hours.

5 Stripped 3X from methylene chloride then dissolved in methylene chloride and rinsed 3X with saturated NaHCO₃, 1X with brine. Dried and stripped in vacuo to give 250 mg of amber solids as product. LCMS detects (M+H)⁺ = 227.

10

Example 112 Part C. Preparation of 1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-(3S)-3-(6-tert-butyl-thieno[3,2-d]pyrimidin-4-ylamino)-pyrrolidin-2-one, TFA salt

15

Followed the procedure of Example 106 Part C starting from (3S)-3-amino-1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-pyrrolidin-2-one and 6-tert-butyl-4-chloro-thieno[3,2-d]pyrimidine. Purified by HPLC to give 6.0 mg
20 of white solids as title product. LCMS detects (M+H)⁺ = 598.

Example 113

25 Part A. Preparation of 6-tert-Butyl-2-trifluoromethyl-thieno[3,2-d]pyrimidin-4-ol

3-Amino-5-tert-butyl-thiophene-2-carboxylic acid methyl ester (0.50 g, 2.34mmol, 1 eq.) and trifluoroacetamidine
30 (263 mg, 2.34 mmol, 1 eq.) were heated neat at 150 °C until reaction was complete by TLC. Cooled to rt then dissolved resultant solids in chloroform. Dried and

stripped in vacuo to give 540 mg of white solids as product. LCMS detects (M+H)+ = 277.

5 Part B. Preparation of 6-tert-Butyl-4-chloro-2-
trifluoromethyl-thieno[3,2-d]pyrimidine

Followed the procedure of Example 112 Part B starting from 6-tert-Butyl-2-trifluoromethyl-thieno[3,2-
10 d]pyrimidin-4-ol. LCMS detects (M+H)+ = 295.

Example 113 Part C Preparation of 1-[(1S, 2R, 4R)-2-
benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-
cyclohexyl]- (3S)-3-(6-tert-butyl-2-trifluoromethyl-
15 thieno[3,2-d]pyrimidin-4-ylamino)-pyrrolidin-2-one, TFA
salt

Followed the procedure of Example 106 Part C starting from 6-tert-butyl-4-chloro-2-trifluoromethyl-thieno[3,2-
20 d]pyrimidine. Purified by HPLC. LCMS detects (M+H)+ = 666.

Example 114

25 Part A. Preparation of Ethyl 3-(tert-Butyl)-pyrrole-5-
carboxylate

The above compound was synthesized by the methods disclosed in Example 129 employing tert-butylchloride in
30 place of 1-chloroadamantane and foregoing the initial 30 minute heating period. MS found: (M+H)+ = 196.28.

Part B. Preparation of Ethyl 3-tert-Butyl-1-aminopyrrole-5-carboxylate.

Preparation of monochloramine by the method of John
5 Hynes, Jr., et al., J. Org. Chem., 2004, in press: NH_4Cl
(3 g, 56 mmol, was mixed in ether (110 mL) and cooled to
-5 °C. Concentrated NH_4OH (4.7 mL) was then added
followed by dropwise addition of bleach (Chlorox, 72 mL)
over 15 minutes. The mixture was stirred for 15 minutes,
10 the layers separated and the organic layer washed with
brine. The organic layer was dried over powdered CaCl_2 in
the freezer for 1h and used for the subsequent step
immediately.

Ethyl 3-(tert-butyl)pyrrole-5-carboxylate (obtained
15 from Part A) (1.67 g, 8.6 mmol, 1 eq) was dissolved in
DMF. Sodium hydride (60% suspension in oil) (0.41 g, 10
mmol, 1.2 eq) was then added thereto cautiously and
stirred for 45 minutes at RT under nitrogen.
Monochloramine was then added (0.15M in ether, 68.4 mL,
20 10 mmol, 1.2 eq). The next morning, the reaction is
quenched with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$, diluted with
water and extracted into ether. The ether layer is
dried, filtered and stripped to yield 3.19g of product as
a yellow oil which eventually crystallized as long
25 needles. MS found: $(\text{M}+\text{H})^+ = 211.34$.

Part C. Preparation of 6-tert-Butyl-pyrrolo[2,1-f][1,2,4]triazin-4-ol

30 Ethyl 3-tert-Butyl-1-aminopyrrole-5-carboxylate (1.00 g,
4.76 mmol, 1 eq), formamidine acetate (1.46 g, 14.3 mmol,
3 eq.) and ethoxyethanol (10 mL) were mixed and refluxed
for 3 hours. The solvent was stripped and then

restripped from chloroform (3X) to yield a solid. This solid was stirred in 5 mL MeOH, filtered, and the collected solids rinsed with Et₂O and dried to yield 233 mg of a white solid as product. LCMS found: (M+H)⁺ =
5 191.

Part D. Preparation of 6-tert-Butyl-4-chloro-pyrrolo[2,1-f][1,2,4]triazine

10 The compound from Part C immediately above (0.43 mg, 2.26 mmol, 1 eq.) and POCl₃ (4.21 mL, 45.2 mmol, 20 eq.) were mixed and refluxed for 4 hours. The mixture was stripped then restripped 3X from methylene chloride and then dissolved in methylene chloride and rinsed 3X with sat'd
15 NaHCO₃, 1X with brine. Dried and stripped in vacuo to give 490 mg of an amber oil. LCMS detects (M+H)⁺ = 210.

Example 114 Part E. Preparation of 1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-
20 cyclohexyl]-(3S)-3-(6-tert-butyl-pyrrolo[2,1-f][1,2,4]triazin-4-ylamino)-pyrrolidin-2-one

The above compound was synthesized using the procedure of Example 106 Part C starting from 6-tert-Butyl-4-
25 chloro-pyrrolo[2,1-f][1,2,4]triazine. LCMS detects (M+H)⁺ = 581.

Example 115

Part A. Preparation of 6-Adamant-1-yl-4-chloro-pyrrolo[2,1-f][1,2,4]triazine
30

The above compound was prepared from ethyl 3-(adamanty-1-yl)-pyrrole-5-carboxylate by the procedures in Example

114, parts A,B, and C beginning with ethyl 3-(Adamanty-1-yl)-pyrrole-5-carboxylate (Example 129). Mass found: $(M+H)^+ = 288.22$.

5

Example 115 Part B. Preparation of (3S)-3-(6-Adamantan-1-yl-pyrrolo[2,1-f][1,2,4]triazin-4-ylamino)-1-[(1S,2R,4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-pyrrolidin-2-one.

10

3S-3-Amino-1-[(1S,2R,4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-pyrrolidin-2-one (49 mg, 0.12 mmol, 1 eq), 6-adamant-1-yl-4-chloro-pyrrolo[2,1-f][1,2,4]triazine (46 mg, 0.18 mmol, 1.5 eq),
 15 triethylamine (0.066 mL, 0.48 mmol, 4 eq) and ethanol (1.7 mL) were microwaved at 100 °C for 1 hour. The contents were stripped and flash chromatographed in 100% EtOAc to 4:1 chloroform/methanol to yield 49 mg of a white powder. This powder was taken up in methylene
 20 chloride and washed with water (3X) . The organic layer was dried and stripped to yield 30 mg of a white powder. Mass found: $(M+H)^+ = 659.49$.

Example 116

25 Part A. Preparation of 2-Phenyl-3H-imidazole-4-carboxylic acid methyl ester

Phenylamidoxime (5.00 g, 36.7 mmol, 1 eq.), methyl propiolate (3.27 mL, 36.7 mmol, 1 eq.), and methanol (25
 30 mL) were refluxed overnight under nitrogen. The reaction was stripped 2X from toluene. Added diphenyl ether (20 mL then heated at 200 °C overnight. Cooled to rt. Added ethyl acetate (50 mL). Rinsed 2X with brine. The

organic layer was dried and stripped in vacuo to give an amber oil. Triturated solids with diethyl ether. Obtained 2.84 g of tan solids as product. LCMS detects (M+H)⁺ = 203.

5

Part B. Preparation of 3-Methyl-2-phenyl-3H-imidazole-4-carboxylic acid methyl ester and 1-Methyl-2-phenyl-1H-imidazole-4-carboxylic acid methyl ester

10 2-Phenyl-3H-imidazole-4-carboxylic acid methyl ester (250 mg, 1.24 mmol, 1 eq.) was dissolved in THF (10 mL) at rt under nitrogen then cooled to 0 °C. Potassium hexamethyldisilazane (0.5 M in toluene) (2.72 mL, 1.36 mmol, 1.1 eq.) was added dropwise via an addition funnel.
15 Stirred 10 minutes. Added iodomethane (85 mL, 1.36 mmol, 1.1 eq.). Stirred overnight at rt. Added saturated NH₄Cl (20 mL), and extracted 2X with methylene chloride. The organic layers were combined, dried and stripped in vacuo to give 225 mg of an amber oil as product. LCMS detects
20 (M+H)⁺ = 217.

Part C. Preparation of 3-Methyl-2-phenyl-3H-imidazole-4-carboxylic acid and 1-Methyl-2-phenyl-1H-imidazole-4-carboxylic acid

25 3-Methyl-2-phenyl-3H-imidazole-4-carboxylic acid methyl ester and its isomer (225 mg, 1.04 mmol, 1 eq.), 4 N NaOH (1.30 mL, 5.20 mmol, 5 eq.) and THF (5 mL) were mixed at rt then refluxed for 2 hours then stirred overnight at rt. Stripped off the THF, added water then rinsed 1X
30 with diethyl ether. The basic aqueous pH was adjusted to 3 with conc. HCl. The aqueous was then extracted 3X with chloroform (10 mL). The chloroform layers were combined,

dried and stripped in vacuo to give 30 mg of a film as product. LCMS detects (M+H)⁺ = 203.

Example 116 Part D. Preparation of 3-Methyl-2-phenyl-3H-imidazole-4-carboxylic acid {(3S)-1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-2-oxo-pyrrolidin-3-yl}-amide, TFA salt and 1-Methyl-2-phenyl-1H-imidazole-4-carboxylic acid {(3S)-1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-2-oxo-pyrrolidin-3-yl}-amide

(3S)-3-Amino-1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-pyrrolidin-2-one (and other isomer) (50 mg, 0.124 mmol, 1 eq.), 3-methyl-2-phenyl-3H-imidazole-4-carboxylic acid (30 mg, 0.148 mmol, 1.2 eq.), 1-hydroxybenzotriazole hydrate (HOBT) (20 mg, 0.148 mmol, 1.2 eq.), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide HCl (EDCI) (28 mg, 0.148 mmol, 1.2 eq.), triethylamine (35 μ L, 0.247 mmol, 2 eq.) and THF (5 mL) were stirred at rt under nitrogen overnight. Purified by LCMS. Obtained 50 mg of white solids as product. LCMS detects (M+H)⁺ = 592.

Example 117

Part A. Preparation of 3-Benzyl-2-phenyl-3H-imidazole-4-carboxylic acid methyl ester and 1-Benzyl-2-phenyl-1H-imidazole-4-carboxylic acid methyl ester

2-Phenyl-3H-imidazole-4-carboxylic acid methyl ester (250 mg, 1.24 mmol, 1 eq.) was dissolved in THF (10 mL) at rt under nitrogen then cooled to 0 °C. Potassium

hexamethyldisilazane (0.5 M in toluene) (2.72 mL, 1.36 mmol, 1.1 eq.) was added dropwise via an addition funnel. Stirred 10 minutes. Added benzylbromide (0.16 mL, 1.36 mmol, 1.1 eq.). Stirred overnight at rt. Added
5 saturated NH_4Cl (20 mL), and extracted 2X with methylene chloride. The organic layers were combined, dried and stripped in vacuo to give 200 mg of an amber oil as product. LCMS detects $(\text{M}+\text{H})^+ = 293$.

10

Part B. Preparation of 3-Benzyl-2-phenyl-3H-imidazole-4-carboxylic acid and 1-Benzyl-2-phenyl-1H-imidazole-4-carboxylic acid

15 3-Benzyl-2-phenyl-3H-imidazole-4-carboxylic acid methyl ester (200 mg, 0.684 mmol, 1 eq.) and other isomer, 4 N NaOH (0.86mL, 3.42 mmol, 5 eq.) and THF (5 mL) were mixed at rt then refluxed for 2 hours then stirred overnight at rt. Stripped off the THF, added water then rinsed 1X
20 with diethyl ether. The basic aqueous pH was adjusted to 3 with conc. HCl. The aqueous was then extracted 3X with chloroform (10 mL). The chloroform layers were combined, dried and stripped in vacuo to give 390 mg of an amorphous solid as product. LCMS detects $(\text{M}+\text{H})^+ = 279$.

25

Example 117 Part C. Preparation of 3-Benzyl-2-phenyl-3H-imidazole-4-carboxylic acid {(3S)-1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-2-oxo-pyrrolidin-3-yl}-amide, TFA salt and 1-
30 Benzyl-2-phenyl-1H-imidazole-4-carboxylic acid {(3S)-1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-2-oxo-pyrrolidin-3-yl}-amide, TFA salt

Followed the procedure of Example 116, Part D starting from (3S)-3-amino-1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-pyrrolidin-2-one and 3-benzyl-2-phenyl-3H-imidazole-4-carboxylic acid and its other isomer. Obtained 21 mg of off-white solids as product. LCMS detects (M+H)+ = 668.

10

Example 118

Preparation of 2-Phenyl-3H-imidazole-4-carboxylic acid

{(3S)-1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-2-oxo-pyrrolidin-3-yl}-amide, TFA salt

15

3-Benzyl-2-phenyl-3H-imidazole-4-carboxylic acid {(3S*)-1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-2-oxo-pyrrolidin-3-yl}-amide and its other isomer (15 mg) 5 mL methanol, and 20% Pd(OH)₂ (10 mg) were hydrogenated until completion by TLC on a Parr shaker at 50 psi. Filtration through fiberglass filter paper under nitrogen and removal of solvent in vacuo yielded 6 mg of product. LCMS detects (M+H)+ = 578.

25

Example 119

Part A. Preparation of 6,7-Dimethoxy-quinazolin-4-ol

30

Followed the procedure of Example 107 Part A starting from 2-amino-4,5-dimethoxy-benzoic acid. . LCMS detects (M+H)+ = 207.

Part B. Preparation of 4-Chloro-6,7-dimethoxy-quinazoline

5 6,7-Dimethoxy-quinazolin-4-ol (1.00 g, 4.85 mmol, 1 eq.),
phosphorous oxychloride (4.07 mL, 43.6 mmol, 9.00 eq.)
and triethylamine (6.08 mL, 43.6 mmol, 9 eq.) were
refluxed for 2 hours. Stripped then restripped 3X from
methylene chloride then dissolved in methylene chloride
10 and rinsed 3X with saturated sodium bicarbonate, 1X with
brine. Dried and stripped in vacuo to give an amber oil.
Purified over silica gel in 9:1 to 3:1 Hexanes/EtOAc.
Obtained 0.84 g of off-white solids as product. LCMS
detects (M+H)+ = 225.

15

Example 119 Part C. Preparation of 1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-(3S)-3-(6,7-dimethoxy-quinazolin-4-ylamino)-pyrrolidin-2-one, TFA salt

20

Followed the procedure of Example 106 Part C starting
from (3S)-3-Amino-1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-pyrrolidin-2-one and 4-chloro-6,7-dimethoxy-
25 quinazoline. LCMS detects (M+H)+ = 596.

Example 120

Part A. Preparation of 6-Fluoro-quinazolin-4-ol

30

Followed the procedure of Example 107 Part A starting
with 2-amino-5-fluorobenzoic acid. ¹H NMR (400 MHz)

(CD3OD) δ 8.06 (s, 1H), 7.87 (m, 1H), 7.75 (m, 1H), 7.62 (m, 1H).

Part B. Preparation of 4-Chloro-6-fluoro-quinazoline

5

Followed the procedure of Example 112 Part B starting with 6-fluoroquinazolin-4-ol. LCMS detects (M+H)⁺ = 183.

Example 120 Part C. Preparation of 1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-(3S)-3-(6-fluoro-quinazolin-4-ylamino)-pyrrolidin-2-one, TFA salt

15

Followed the procedure of Example 106 Part C starting from (3S)-3-Amino-1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-pyrrolidin-2-one and 4-chloro-6-fluoro-quinazoline. Purified by HPLC. LCMS detects (M+H)⁺ = 554.

20

Example 121

Part A. Preparation of 6-Methyl-quinazolin-4-ol

Followed the procedure of Example 107 Part A starting from 2-Amino-5-methyl-benzoic acid. ¹H NMR (400 MHz) (CD3OD) δ 8.00 (m, 2H), 7.68 (d, 1H, J = 7 Hz), 7.59 (d, 1H, J = 7 Hz), 2.47 (s, 3H).

Part B. Preparation of 4-Chloro-6-methyl-quinazoline

Followed the procedure of Example 111 Part B starting with 6-methylquinazolin-4-ol. LCMS detects (M+H)+ = 179.

5 Example 121 Part B. Preparation of 1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-(3S)-3-(6-methyl-quinazolin-4-ylamino)-pyrrolidin-2-one, TFA salt

10 Followed the procedure of Example 106 Part C starting from (3S)3-amino-1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-pyrrolidin-2-one and 4-chloro-6-methyl-quinazoline. Purified by HPLC. LCMS detects (M+H)+ = 550.

15 **Example 122**

Part A. Preparation of 6-Phenyl-thieno[2,3-d]pyrimidin-4-ol

20 Followed the procedure of Example 112 Part A starting from 2-Amino-5-phenyl-thiophene-3-carboxylic acid methyl ester. LCMS detects (M+H)+ = 229.

Part B. Preparation of 4-Chloro-6-phenyl-thieno[2,3-d]pyrimidine

25 Followed the procedure of Example 112 Part B starting with 6-Phenyl-thieno[2,3-d]pyrimidin-4-ol. LCMS detects (M+H)+ = 247.

30 Example 122 Part C. Preparation of 1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-(3S)-3-(6-phenyl-thieno[2,3-d]pyrimidin-4-ylamino)-pyrrolidin-2-one, TFA salt

Followed the procedure of Example 106 Part C starting from (3S)-3-Amino-1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-pyrrolidin-2-one and of 4-chloro-6-phenyl-thieno[2,3-d]pyrimidine. Purified by HPLC. LCMS detects (M+H)⁺ = 618.

Example 123

10 Part A. Preparation of 2-Butyrylamino-5-chloro-benzamide

2-Amino-5-chlorobenzamide (1.10 g, 6.5 mmol, 1 eq.), 1.000 N NaOH (6.50 mL, 6.5 mmol, 1 eq.) and THF (20 mL) were mixed and stirred at 0 °C. To this mixture was added
15 butyryl chloride dropwise (0.68 mL, 6.50 mmol, 1 eq.). More acid chloride and base were added to drive reaction to completion. The reaction was allowed to warm to rt. After 4 days the reaction was worked up by adding ethyl acetate, washing with 1 N HCl (3X), saturated sodium
20 bicarbonate (1X), and brine (1X). The organic layer was dried and stripped to yield 1.44 g of a white powder as product. LCMS detects (M+H)⁺ = 241.0.

25 Part B. Preparation of 6-Chloro-2-propyl-quinazolin-4-ol

2-Butyrylamino-5-chloro-benzamide (1.08 g, 4.49 mmol, 1 eq.), 1.000 N NaOH (13.46 mL, 13.5 mmol, 3 eq.) and ethanol (10 mL) were mixed and stirred at rt for 15 minutes. The mixture was acidified to pH = 2 with 1.000
30 N HCl. The mixture was extracted with ethyl acetate. Solids that did not dissolve were filtered and rinsed

with diethyl ether to dry. Obtained 810 mg of a white solid product. LCMS detects (M+H)⁺ = 223.

Part C Preparation of 4,6-Dichloro-2-propyl-quinazoline

5
6-Chloro-2-propyl-quinazolin-4-ol (810 mg, 3.64 mmol, 1 eq.), phosphorous oxychloride (3.30 mL, 35.1 mmol, 9.64 eq.) and triethylamine (1.63 mL, 11.7 mmol, 3.21 eq.) were refluxed for 2 hours. Stripped 3X from methylene chloride then dissolved in methylene chloride and rinsed 10 3X with saturated sodium bicarbonate, 1X with brine. Dried and stripped in vacuo to give an amber oil. Purified over silica gel in 9:1 Hexanes/EtOAc. Obtained 510 mg of off-white solids as product. The product was 15 used immediately in Example 121 Part D.

Example 123 Part D. Preparation of 1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-(3S)-3-(6-chloro-2-propyl-pyrido[2,3-
20 d]pyrimidin-4-ylamino)-pyrrolidin-2-one, TFA salt.

1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-(3S)-3-(6-chloro-2-propyl-pyrido[2,3-d]pyrimidin-4-ylamino)-pyrrolidin-2-one, TFA salt was prepared from (3S)-3-amino-1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-pyrrolidin-2-one and 4,6-dichloro-2-propyl-quinazoline using the conditions described in Example 106 Part C. MS (ES⁺) = 613 (M + H)⁺.

30

Example 124

Part A. Preparation of 1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-(3S)-3-(6-chloro-2-isopropyl-quinazolin-4-ylamino)-pyrrolidin-2-one, TFA salt

- 5 The above compound was synthesized from isobutyryl chloride using the procedures found in Example 123, Parts A-D. MS (ES+) = 612 (M + H)⁺.

Example 125

- 10 Preparation of 1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-(3S)-3-(2-tert-butyl-6-chloro-quinazolin-4-ylamino)-pyrrolidin-2-one, TFA salt

- 15 The above compound was synthesized from 2,2-Dimethyl-propionyl chloride using the procedures found in Example 123, Parts A-D. LCMS detects (M+H)⁺ = 626.

Example 126

- 20 Part A. Preparation of 6-Chloro-2-methyl-quinazolin-4-ol

2-Amino-5-chlorobenzoic acid (3.58 g, 20.9 mmol, 1 eq.), acetamidine hydrochloride (2.36 g, 25.1 mmol, 1.2 eq.) and 2-ethoxyethanol (70 mL) were mixed and refluxed for 48 h.

- 25 The resultant solids were filtered and dried to yield 1.57 g of yellow solid product. MS (ES+) = 195/197 (M + H)⁺.

Part B. Preparation of 4,6-Dichloro-2-methyl-quinazoline

30

6-Chloro-2-methyl-quinazolin-4-ol (0.75 g, 3.90 mmol, 1 eq.), phosphorous oxychloride (3.47 mL, 37.4 mmol, 9.64 eq.) and triethylamine (1.62 mL, 12.5 mmol, 3.21 eq.)

were refluxed for 4 hours. The mixture was stripped twice from toluene and the residue dissolved in ethyl acetate. The organic layer was washed with saturated NH_4Cl (2X), dried and stripped. The residue was flash
5 chromatographed in 3:2 ethyl acetate/hexanes to yield 400 mg of a light yellow solid product. MS (ES+) = 213/215/217 (M + H)⁺.

Example 126 Part C. Preparation of 1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-(3S)-3-(6-chloro-2-methyl-quinazolin-4-ylamino)-pyrrolidin-2-one
10

The above compound was synthesized following the
15 procedure of Example 106 Part C using the product from Part B immediately above. MS (ES+) = 585 (M + H)⁺.

Example 127

Preparation of 1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-(3S)-3-(6-chloro-2-ethyl-quinazolin-4-ylamino)-pyrrolidin-2-one
20

The above compound was synthesized by the procedures in Example 126 beginning with propionamidinium hydrochloride.
25 MS (ES+) = 599 (M + H)⁺.

Example 128

Part A. Preparation of {(3S)-1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-2,5-dioxo-pyrrolidin-3-yl}-carbamic acid tert-butyl ester

5

(1S, 2R, 4R)-2-Benzenesulfonylmethyl-N4-isopropyl-N4-methyl-cyclohexane-1,4-diamine (300 mg, 0.93 mmol, 1 eq.), L-N-BOC-Aspartic acid (216 mg, 0.93 mmol, 1.0 eq.), 1-hydroxybenzotriazole hydrate (HOBT) (275 mg, 2.03 mmol, 2.2 eq.), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide HCl (EDCI) (390 mg, 2.03 mmol, 2.2 eq.), triethylamine (0.39 mL, 2.77 mmol, 3 eq.) and methylene chloride (15 mL) were stirred at 0 °C and allowed to warm to rt under nitrogen overnight. The mixture was washed with 2 N sodium carbonate, water (1X) and the organic layer dried and stripped. The residue was purified over silica gel in 100 % ethyl acetate to 4:1 methylene chloride/methanol to 4:1 methylene chloride/2N NH₃ in methanol. Obtained 60 mg of product. LCMS detects (M+H)⁺ = 522.

20

Part B. Preparation of (3S)-3-Amino-1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-pyrrolidine-2,5-dione

{(3S)-1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-2,5-dioxo-pyrrolidin-3-yl}-carbamic acid tert-butyl ester (60 mg), TFA (1 mL), and methylene chloride (3 mL) were mixed and stirred overnight at rt. The mixture was stripped and restripped from methylene chloride (3X) to yield 60 mg of an oil. LCMS detects (M+H)⁺ = 374.

30

Example 128 Part C. Preparation of N-{(3S)-1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-2,5-dioxo-pyrrolidin-3-yl}-3-trifluoromethyl-benzamide, TFA salt

5

(3S)-3-Amino-1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-pyrrolidine-2,5-dione (60 mg, 0.092 mmol, 1 eq), 3-trifluoromethylbenzoyl chloride (0.014 mL, 0.092 mmol, 1 eq.), triethylamine
 10 (0.039 mL, 0.28 mmol, 3 eq.) and THF (3 mL) were mixed and stirred at rt with the acid chloride being added last. The reaction mixture was stripped and purified by LCMS to yield 5.5 mg of product. LCMS detects (M+H)+ = 594.

15

Example 129

Part A. Preparation of Ethyl 3-(Adamanty-1-yl)-pyrrole-5-carboxylate

20 Ethyl pyrrole-2-carboxylate (2.09 g, 15 mmol, 1 eq), was added to a mixture of gallium(III) chloride (2.90 g, 16.5 mmol, 1.1 eq) in carbon disulfide (40 mL) and the contents heated at 40 °C for 30 min. Afterwards, 1-chloroadamantane (2.82 g, 16.5 mmol, 1.1 eq), was added
 25 thereto and the contents heated for another 40 minutes. The reaction was poured onto a mixture of ice and 1N HCl, and extracted with chloroform. The extracts were washed with saturated sodium bicarbonate, dried (MgSO₄) and the solvent stripped to yield a crude solid.
 30 Recrystallization from EtOAc yielded 2 crops. 1st crop

wt. = 0.67 grams. 2nd crop wt. = 1.10 grams. MS found:
(M+H)⁺ = 274.44 and 274.45, respectively.

5 Part B. Preparation of 3-(Adamanty-1-yl)-pyrrole-5-
carboxylic Acid

The compound obtained from Part A immediately above
(0.29 g, 1.1 mmol, 1 eq), 1.000 N NaOH (2.20 mL, 2.2
mmol, 2 eq) and MeOH (15 mL) were mixed and stirred
10 overnight. After only partial reaction, more 1.000 N
NaOH (21 mL) together with more MeOH to dissolve were
added and the contents refluxed for 4 hours. The
contents were acidified to pH=1 with 1N HCl. The MeOH
was stripped off to yield solids and aqueous. The
15 mixture was extracted with EtOAc, the EtOAc layers were
combined, washed with brine, dried (MgSO₄) and stripped
to yield 250 mg of a white powder. MS found: (M+H)⁺
=246.44.

20 Example 129 Part C. Preparation of N-{(3S)-1-[-
(1S,2R,4R)-2-Benzenesulfonylmethyl-4-(isopropyl-methyl-
amino)-cyclohexyl]-2-oxo-pyrrolidin-3-yl}-4-adamantan-1-
yl-1H-pyrrole-2-carboxamide, TFA salt.

25 (3S)-1-[1S,2R,4R-2-benzenesulfonylmethyl-4-(isopropyl-
methyl-amino)-cyclohexyl]-pyrrolidin-2-one (45 mg, 0.11
mmol, 1 eq), 3-(adamanty-1-yl)-pyrrole-5-carboxylic acid
(27 mg, 0.11 mmol, 1 eq), HOBT (15 mg, 0.11 mmol, 1 eq),
1-[3-(dimethylaminopropyl)]-3-ethylcarbodiimide
30 hydrochloride (EDCI) (21 mg, 0.11 mmol, 1 eq), and
methylene chloride (5 mL) were mixed and stirred
overnight. The contents were stripped and purified by

LCMS. Lyophilization yielded 45 mg of a white solid. MS found: $(M+H)^+ = 635.58.s$

5

Example 130

Part A. Preparation of Ethyl 3-(Adamanty-1-yl)-1-methylpyrrole-5-carboxylate

Ethyl 3-(adamanty-1-yl)-pyrrole-5-carboxylate
10 (obtained from Example 129) (0.20 g, 0.7 mmol, 1 eq) was dissolved in THF (20 mL). Potassium bis(trimethylsilyl)amide (0.5 M in Tol, 1.62 mL, 0.81 mmol, 1.1 eq) was added thereto followed by iodomethane (0.102 mL, 1.6 mmol, 2.2 eq). The next day, the same
15 amounts of potassium bis(trimethylsilyl)amide and iodomethane were again added to drive the reaction to completion. In 4h, the reaction was finished. Ethyl acetate was added (100 mL) and the organic layer was washed with water (2x), brine, dried (MgSO₄) and stripped
20 to yield 600 mg of product which was used as is in the next step. MS found: $(M+H)^+ = 288.16$.

Part B. Preparation of 3-(Adamanty-1-yl)-1-methylpyrrole-5-carboxylate

25

Saponification of ethyl 3-(Adamanty-1-yl)-1-methylpyrrole-5-carboxylate (entire contents from Part A) by the procedure in Example 129 Part B yielded 160 mg of product. MS found: $(M-H)^+ = 258.10$.

30

Example 130 Part C. Preparation of N-((3S)-1-[-(1S,2R,4R)-2-Benzenesulfonylmethyl-4-(isopropyl-methyl-

amino)-cyclohexyl]-2-oxo-pyrrolidin-3-yl}-4-adamantan-1-yl-1-methyl-1H-pyrrole-2-carboxamide, TFA salt.

(3S)-3-Amino-1-[(1S,2R,4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-pyrrolidin-2-one (49 mg, 0.12 mmol, 1 eq), 3-(adamanty-1-yl)-pyrrole-5-carboxylic acid (31 mg, 0.12 mmol, 1 eq), HOBt (16 mg, 0.12 mmol, 1 eq), 1-[3-(dimethylaminopropyl)]-3-ethylcarbodiimide hydrochloride (EDCI) (23 mg, 0.11 mmol, 1 eq), and methylene chloride (5 mL) were mixed and stirred overnight. The contents were stripped and dissolved in EtOAc, washed with 1N HCl (1X), 1N NaOH (2X), brine (1X), dried and stripped. The residue was flash chromatographed in 1:1 hexane/ EtOAc to 100% EtOAc to 4:1 chloroform/methanol to yield 31 mg of a yellow glass. MS found: (M+H)+ = 649.32.

Example 131

20 Part A. Preparation of 5-Bromo-2-tert-butyl-pyrimidine-4-carboxylic acid.

A 22% solution of sodium ethoxide in ethanol (53 mL, 165 mMol) was added dropwise to a magnetically stirred suspension of tert-butylcarbamidine hydrochloride (20.0 g, 146 mMol) in ethanol (100 mL). When the addition was complete, the yellow suspension was warmed to 50° C, the heating mantle was removed, and a solution of mucobromic acid (15.7 g, 61 mMol) in ethanol (50 mL) was added dropwise at a rate which did not allow the temperature to exceed 55° C. When this addition was complete, a 22% solution of sodium ethoxide in ethanol (32 mL, 98 mMol)

was added dropwise, then the mixture was allowed to cool to room temperature. The suspension was filtered, the solids were rinsed with ethanol (2 x 20 mL), and the combined filtrates were concentrated *in-vacuo*. The residue thus obtained was stirred in 2 N aqueous HCl (30 mL). The resulting solids were collected by filtration, rinsed with ice-cold water (2 x 20 mL), and air dried to yield 12.1 g of a beige powder as product. MS (ES+) = 259, 261 (M + H)⁺. Yield = 76%.

10

Part B. Preparation of 5-Bromo-2-tert-butyl-pyrimidine-4-carboxylic acid methyl ester.

A 2.0 M hexanes solution of trimethylsilyldiazomethane (11.8 mL, 23.62 mMol) was added dropwise to a stirring solution of 5-bromo-2-tert-butyl-pyrimidine-4-carboxylic acid (6.12 g, 23.62 mMol) in 9 : 1 benzene/methanol (100 mL), and the reaction was stirred for 2 days. TLC analysis showed that the reaction was complete, so the mixture was concentrated *in-vacuo*. The residue was dissolved in ethyl acetate (100 mL), washed with water (3 x 20 mL), dried over sodium sulfate, then concentrated *in-vacuo*. Purified over silica gel, eluting with 10% ethyl acetate/hexanes, to yield 5.2 g of a colorless oil as product. MS (ES+) = 273, 275 (M + H)⁺. Yield = 81%.

20

25

Part C. Preparation of 5-tert-Butoxycarbonylamino-2-tert-butyl-pyrimidine-4-carboxylic acid methyl ester.

A flame dried reaction tube charged with tert-butylcarbamate (140 mg, 1.2 mMol), cesium carbonate (456 mg, 1.4 mMol), 4,5-bis(diphenylphosphino)-9,9-

30

dimethylxanthane (18 mg, 0.03 mMol), and
tris(dibenzylideneacetone)dipalladium(0) (19 mg, 0.02
mMol) was evacuated under vacuum, then backfilled with
argon. Dioxane (2 mL) and 5-bromo-2-tert-butyl-
5 pyrimidine-4-carboxylic acid methyl ester (273 mg, 1.0
mMol) were added, and the mixture was degassed under
vacuum. The tube was then backfilled with argon, sealed,
and heated at 100° C for 2 hours. Analysis by LC/MS
showed complete consumption of starting bromide. The
10 mixture was diluted with methylene chloride (20 mL),
filtered to remove solids, and concentrated *in-vacuo*.
The residue was purified over silica gel, eluting with
10% ethyl acetate/heptane, to yield 152 mg of white
solids as product. MS (ES+) = 310 (M + H)⁺. Yield = 50%.

15

Part D. Preparation of 5-Amino-2-tert-butyl-pyrimidine-
4-carboxylic acid methyl ester, HCl salt.

5-tert-Butoxycarbonylamino-2-tert-butyl-pyrimidine-4-
20 carboxylic acid methyl ester (2.4 g, 7.75 mMol) was
dissolved in a 4 M solution of HCl in dioxane (30 mL).
After 10 minutes of stirring, a thick white solid
precipitated. The reaction was allowed to stir
overnight, during which time the mixture became a
25 homogenous, amber solution. Concentrated *in-vacuo*, and
the residue was stripped from toluene (2 x 50 mL)
followed by methylene chloride (3 x 50 mL) to remove
excess HCl. The resulting 1.85 g of yellow solids was
used without further purification in the next step. MS
30 (ES+) = 210 (M + H)⁺.

Part E. Preparation of 6-tert-Butyl-pyrimido[5,4-d]pyrimidin-4-ol.

A mixture of 5-amino-2-tert-butyl-pyrimidine-4-carboxylic acid methyl ester, HCl salt (1.1 g, 4.48 mMol) and formamidine acetate (1.86 g, 17.90 mMol) in 2-ethoxyethanol (20 mL) was heated at reflux for 5 hours. LC/MS analysis showed the reaction to be essentially complete, so the mixture was cooled to room temperature, then concentrated *in-vacuo*. The residue was purified over silica gel, eluting with ethyl acetate, 1% methanol/ethyl acetate, then 2% methanol/ethyl acetate to yield 1.06 g of a beige solid as product. MS (ES+) = 205 (M + H)⁺. Yield = 94%.

Part F. Preparation of 2-tert-Butyl-8-chloro-pyrimido[5,4-d]pyrimidine.

6-tert-Butyl-pyrimido[5,4-d]pyrimidin-4-ol (210 mg, 1.03 mMol) was dissolved in phosphorous oxychloride (10 mL), and the mixture was heated at reflux for 4 hours. The solution was concentrated *in-vacuo*, then stripped from methylene chloride (3 x 50 mL) to remove excess phosphorous oxychloride. The residue was stirred for 10 minutes in saturated sodium bicarbonate (50 mL), then extracted with ethyl acetate (3 x 30 mL). The combined organic phases were washed with water (30 mL), followed by brine (30 mL), dried over sodium sulfate, then concentrated *in-vacuo*. The residue was purified over silica gel, eluting with 50% ethyl acetate/heptane, to yield 150 mg of a white solid as product. NMR (500 MHz, CDCl₃) δ 9.61 (s, 1H), 9.15 (s, 1H), 1.52 (s, 9H).

Example 131 Part G. Preparation of 1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-(3S)-3-(6-tert-butyl-pyrimido[5,4-d]pyrimidin-4-ylamino)-pyrrolidin-2-one, TFA salt.

The titled compound was prepared from (3S)-3-amino-1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-pyrrolidin-2-one and 2-tert-butyl-8-chloro-pyrimido[5,4-d]pyrimidine using the conditions described in JBS Example 106, Part C. MS (ES+) = 594 (M + H)⁺.

Example 132

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Example 132 Preparation of 5-Bromo-2-tert-butyl-pyrimidine-4-carboxylic acid {(3S)-1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-2-oxo-pyrrolidin-3-yl}-amide, TFA salt.

20

(3S)-3-Amino-1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-pyrrolidin-2-one (93 mg, 0.23 mMol), 5-bromo-2-tert-butyl-pyrimidine-4-carboxylic acid, (60 mg, 0.23 mMol), HOBT (68 mg, 0.50 mMol), triethylamine (96 μ L, 0.69 mMol), and EDCI (96 mg, 0.50 mMol) were combined in CH₂Cl₂ (2 mL), and the mixture was stirred overnight at room temperature. The mixture was diluted with ethyl acetate (15 mL), and washed with saturated NaHCO₃ (3 x 5 mL), water (5 mL), and brine (5 mL). The organic phase was dried over sodium sulfate, and concentrated *in-vacuo*. The residue was purified by reverse phase HPLC, using a Phenomenex Luna 10 μ , C18

(2), 250 x 50 mm column, under the following conditions: 10% to 70% acetonitrile in water (0.05% TFA in each solvent) over 30 minutes. The reaction yielded 13 mg of white powder as product. MS (ES+) = 570 (M + H).

5

Example 133

Preparation of 2-tert-Butyl-pyrimidine-4-carboxylic acid
{(3S*)-1-[(1S*, 2R*, 4R*)-2-benzenesulfonylmethyl-4-
(isopropyl-methyl-amino)-cyclohexyl]-2-oxo-pyrrolidin-3-
 10 yl}-amide, TFA salt.

A solution of 5-bromo-2-tert-butyl-pyrimidine-4-carboxylic acid {(3S)-1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-
 15 cyclohexyl]-2-oxo-pyrrolidin-3-yl}-amide, TFA salt (30 mg, 0.04 mMol) in methanol (10 mL) was hydrogenated at 50 psi in the presence of 1 N aqueous sodium hydroxide (80 µL, 0.08 mMol) and 10% palladium on activated carbon (20 mg) for 2 hours. The catalyst was removed by filtration,
 20 and the filtrate was concentrated *in-vacuo*. The residue was purified by reverse phase HPLC, using a Phenomenex Luna 10µ, C18 (2), 250 x 50 mm column, under the following conditions: 10% to 70% acetonitrile in water (0.05% TFA in each solvent) over 30 minutes. The
 25 reaction yielded 25 mg of white powder as product. MS (ES+) = 648 (M + H).

Example 134

Preparation of 2-tert-Butyl-5-phenyl-pyrimidine-4-
 30 carboxylic acid {(3S)-1-[(1S, 2R, 4R)-2-

benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-
cyclohexyl]-2-oxo-pyrrolidin-3-yl}-amide, TFA salt.

5-Bromo-2-tert-butyl-pyrimidine-4-carboxylic acid {(3S)-
5 1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-
methyl-amino)-cyclohexyl]-2-oxo-pyrrolidin-3-yl}-amide,
TFA salt (80 mg, 0.10 mMol), phenyl boronic acid (26 mg,
0.21 mMol), and 2.0 M aqueous K₃PO₄ solution (210 µL, 0.42
mMol) were combined in 2 mL of DMF in a microwave
10 reaction tube, and the solution was degassed under
vacuum, then backfilled with argon.
Tetrakis(triphenylphosphine)palladium(0) (20 mg, 0.01
mMol) was added, and the mixture was again degassed as
described above. The tube was sealed, and the reaction
15 mixture was heated via microwave at 150° C for 30 minutes.
The reaction was cooled, some solids were removed by
filtration and rinsed with ethyl acetate, and the
combined filtrates were concentrated *in-vacuo*. The
residue was purified by reverse phase HPLC, using a
20 Phenomenex Luna 10 µ, C18 (2), 250 x 50 mm column, under
the following conditions: 10% to 70% acetonitrile in
water (0.05% TFA in each solvent) over 30 minutes. The
reaction yielded 27 mg of white powder as product. MS
(ES+) = 646 (M + H).

25

Example 135

Part A. Preparation of 3-tert-Butyl-benzoic acid.

30 A mixture of the commercially available methyl 3-bromo-5-
tert-butylbenzoate (700 mg, 2.58 mMol), aqueous NaOH (1
N, 7.75 mL, 7.75 mMol), and Pearlman's catalyst (100 mg)

in methanol (20 mL) was hydrogenated at 50 psi for 22 hours. The catalyst was removed by filtration and rinsed with a small amount of methanol. The filtrate was concentrated *in-vacuo* to remove methanol, and the aqueous mixture was acidified with 1 N HCl (10 mL), then extracted with ethyl acetate (3 x 20 mL). The combined organic phases were dried over sodium sulfate, then concentrated *in-vacuo*. Analysis of the resulting material by LC/MS showed that the ester had hydrolyzed to the carboxylic acid, but that the bromide was still present. The material was dissolved in methanol (20 mL), and hydrogenated overnight at 50 psi in the presence of 1 N aqueous NaOH (5.2 mL, 5.2 mMol) and 10% palladium on activated carbon (50 mg). Analysis of the crude reaction mixture by LC/MS showed that the bromine was still present, so Pearlman's catalyst (200 mg) was added, and hydrogenation at 50 psi was continued for 23 hours. MS showed that the reaction was now complete, so the reaction was worked up as described previously in this example to yield 376 mg of white powder as product. MS (AP-) = 177 (M - H)⁺. Yield = 81%.

Example 135 Part B. Preparation of N-{(3S)-1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-2-oxo-pyrrolidin-3-yl}-3-tert-butyl-benzamide, TFA salt.

The titled compound was prepared from (3S)-3-amino-1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-pyrrolidin-2-one and 3-tert-Butyl-benzoic acid using the conditions described in Example 132. MS (ES+) = 568 (M + H).

Example 136Part A. Preparation of Lithium 3-bromo-5-tert-butylbenzoate.

5

A solution of the commercially available methyl-3-bromo-5-tert-butylbenzoate (87 mg, 0.32 mMol) in THF (2 mL) was treated with 0.5 N aqueous lithium hydroxide (0.71 mL, 0.35 mMol), and the mixture was stirred at room temperature for six hours. The THF was stripped *in-vacuo*, and the aqueous solution was freeze dried to yield 112 mg of light brown solids. This material was used as-is in the next step.

15 Example 136 Part B. Preparation of N-{(3S)-1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-2-oxo-pyrrolidin-3-yl}-3-bromo-5-tert-butylbenzamide, TFA salt.

20 (3S)-3-Amino-1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-pyrrolidin-2-one (39 mg, 0.10 mMol), lithium-3-bromo-5-tert-butylbenzoate (25 mg, 0.10 mMol), diisopropylethylamine (84 μ L, 0.48 mMol), and HATU (37 mg, 0.10 mMol) were combined in CH₂Cl₂ (2 mL), and the mixture was stirred overnight at room temperature. The mixture was diluted with ethyl acetate (15 mL), and washed with saturated NaHCO₃ (3 x 5 mL), water (5 mL), and brine (5 mL). The organic phase was dried over sodium sulfate, and concentrated *in-vacuo*. The residue was purified by reverse phase HPLC, using a Phenomenex Luna 10 μ , C18 (2), 250 x 50 mm column, under the following conditions: 10% to 70% acetonitrile in

25

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water (0.05% TFA in each solvent) over 30 minutes. The reaction yielded 17 mg of white powder as product. MS (ES+) = 647 (M + H)⁺.

5

Example 137Part A. Preparation of Pyrido[2,3-d]pyrimidin-4-ol.

A mixture of 2-aminonicotinic acid (880 mg, 6.4 mMol) and formamidine acetate (2.0 g, 19.1 mMol) in 2-ethoxyethanol
10 (25 mL) was heated at reflux overnight. The solution was allowed to come to room temperature and stand for 2 hours, then the resulting precipitate was collected by filtration, rinsed with 2-ethoxy ethanol (2 x 5 mL), diethyl ether (20 mL), and air dried to yield 525 mg of a
15 gray powder as product. MS (ES+) = 148 (M + H)⁺. Yield = 56%.

Part B. Preparation of 4-Chloro-pyrido[2,3-d]pyrimidine.

20 A solution of pyrido[2,3-d]pyrimidin-4-ol (490 mg, 3.33 mMol), triethylamine (4.4 mL, 31.6 mMol), and phosphorous oxychloride (2.8 mL, 30 mMol) was heated at reflux for 2 hours. The mixture was concentrated *in-vacuo*, and the residue was stripped from methylene chloride (3 x 50 mL)
25 to remove excess phosphorous oxychloride. The residue was dissolved in ethyl acetate (100 mL), saturated sodium bicarbonate (100 mL) was added carefully, causing vigorous gas evolution, and the mixture was stirred for ten minutes. The layers were separated, the organic
30 phase was washed with saturated sodium bicarbonate (30 mL), water (30 mL), brine (30 mL), dried over sodium sulfate, then concentrated *in-vacuo*. The residue was purified over silica gel, eluting with 40% ethyl

acetate/heptane, to yield 92 mg of a tan solid as product. MS (ES+) = 166 (M + H)⁺. Yield = 17%.

5 Example 137 Part C. Preparation of 1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-(3S)-3-(pyrido[2,3-d]pyrimidin-4-ylamino)-pyrrolidin-2-one, TFA salt.

10 The titled compound was prepared from (3S)-3-amino-1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-pyrrolidin-2-one and 4-Chloro-pyrido[2,3-d]pyrimidine using the conditions described in Example 106, Part C. MS (ES+) = 537 (M + H)⁺.

15 **Example 138**

Part A. Preparation of 2-Amino-nicotinic acid ethyl ester

20 A 60% sodium hydride suspension in mineral oil (1.28 g, 32 mMol) was added to a stirring suspension of 2-aminonicotinic acid (4.21 g, 30 mMol) in DMF (50 mL), and the mixture was gently heated until gas evolution was observed. The suspension was stirred at room temperature for 4 hours, after which a homogeneous amber solution was observed. Iodoethane (4.75 g, 30 mMol) was added, and the mixture was allowed to stir overnight at room temperature. The solution was concentrated *in-vacuo*, the residue was taken up in 9 : 1 ethyl acetate/hexane (200 mL), washed with water (5 x 50 mL), and brine (50 mL), 25 dried over sodium sulfate, then concentrated *in-vacuo*. 30 The residue was purified over silica gel, eluting with 25% - 50% ethyl acetate/hexane, to yield 3.6 g of colorless solids as product. NMR (500 MHz, DMSO) δ 8.20

(dd, 1 H, $J = 5$ Hz, 2 Hz), 8.06 (dd, 1H, $J = 8$ Hz, 2 Hz), 7.16 (s, 2H), 6.63 (dd, 1H, $J = 8$ Hz, 5 Hz), 4.28 (q, 2 H, $J = 7$ Hz), 1.30 (t, 3 H, $J = 7$ Hz). Yield = 72%.

5 Part B. Preparation of 2-Amino-5-chloro-nicotinic acid ethyl ester

A solution of 2-amino-nicotinic acid ethyl ester (3.60 g, 21.7 mMol) in methanol (100 mL) was treated with HCl gas
10 via sparge tube for 5 minutes, causing the colorless solution to turn yellow. The solution was concentrated *in-vacuo*, then stripped from methanol (2 x 50 mL) to remove excess HCl. The residue was dissolved in methanol (100 mL), treated with tert-butyl hypochlorite (2.6 g,
15 23.8 mMol), and the mixture was allowed to stir overnight at room temperature. Analysis by TLC showed that some starting material remained, so additional tert-butyl hypochlorite (0.47 g, 4.3 mMol) was added, and stirring was continued overnight. Analysis by TLC showed that all
20 starting material had been consumed. The solution was concentrated *in-vacuo*, the residue was taken up in methylene chloride (150 mL), washed with saturated sodium bicarbonate (3 x 50 mL), 5% aqueous sodium thiosulfate (3 x 50 mL), water (50 mL), brine (50 mL), dried over sodium
25 sulfate, and concentrated *in-vacuo*. The residue was purified over silica gel, eluting with 20% - 30% ethyl acetate/heptane, to yield 1.50 g of colorless solids as product. MS (AP+) = 201 (M + H)⁺. Yield = 35%.

30 Part C. Preparation of 6-Chloro-pyrido[2,3-d]pyrimidin-4-ol.

A mixture of 2-amino-5-chloro-nicotinic acid ethyl ester (1.5 g, 7.38 mMol) and formamidine acetate (3.1 g, 29.51 mMol) in 2-ethoxyethanol (50 mL) was heated at reflux overnight. The solution was cooled to room temperature, and allowed to stand for 2 hours. The resulting precipitate was collected by filtration, rinsed with a small amount of 2-ethoxyethanol followed by diethyl ether (10 mL), and allowed to air dry. The filtrate was concentrated *in-vacuo*, and the residue was triturated with methylene chloride. The resulting solids were combined with the solids from the earlier filtration, and this material was crystallized from methanol to yield 475 mg of tan needles as product, in three crops. MS (ES+) = 182 (M + H)⁺. Yield = 37%.

15

Part D. Preparation of 4,6-Dichloro-pyrido[2,3-d]pyrimidine.

The titled compound was prepared from 6-Chloro-pyrido[2,3-d]pyrimidin-4-ol using the conditions described in Example 131, Part F. MS (ES+) = 201 (M + H)⁺. Yield = 85%.

Example 138 Part E. Preparation of 1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]- (3S)-3-(6-chloro-pyrido[2,3-d]pyrimidin-4-ylamino)-pyrrolidin-2-one, TFA salt.

The titled compound was prepared from (3S)-3-amino-1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-pyrrolidin-2-one and 4,6-Dichloro-pyrido[2,3-d]pyrimidine using the conditions described in Example 106, part C. MS (ES+) = 572 (M + H)⁺.

Example 139Part A. Preparation of 6-Chloro-2-trifluoromethyl-pyrido[2,3-d]pyrimidin-4-ol.

5

The titled compound was prepared from 2-Amino-5-chloro-nicotinic acid ethyl ester and trifluoromethylacetamide using the conditions described in Example 113, part A. MS (ES+) = 250 (M + H)⁺.

10

Part B. Preparation of 4,6-Dichloro-2-trifluoromethyl-pyrido[2,3-d]pyrimidine.

The titled compound was prepared from 6-Chloro-2-trifluoromethyl-pyrido[2,3-d]pyrimidin-4-ol using the conditions described in Example 131; part F. MS (ES+) = 268 (M + H)⁺.

20 Example 139 Part C. Preparation of 1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-(3S)-3-(6-chloro-2-trifluoromethyl-pyrido[2,3-d]pyrimidin-4-ylamino)-pyrrolidin-2-one.

25 The titled compound was prepared from (3S)-3-amino-1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-pyrrolidin-2-one and 4,6-dichloro-2-trifluoromethyl-pyrido[2,3-d]pyrimidine using the conditions described in Example 106, part C. MS (ES+) = 639 (M + H)⁺.

30

Example 140

Part A. Preparation of (4-Trifluoromethoxy-phenyl)-
carbamic acid tert-butyl ester.

A solution of 4-(trifluoromethyl)phenyl isocyanate (9.75
5 g, 48.0 mMol) in THF (100 mL) was cooled to 0° C, and a
1.0 M THF solution of potassium tert-butoxide (53 mL, 53
mMol) was added dropwise. The mixture was allowed to
warm to room temperature, and stirred for 7 hours. The
solution was poured into a mixture of saturated ammonium
10 chloride solution (200 mL), and diethyl ether (200 mL).
Enough water was added to redissolve the ammonium
chloride that had crashed out, the mixture was shaken in
a separatory funnel, and the layers were separated. The
organic phase was washed with saturated ammonium chloride
15 (100 mL), water (100 mL), brine (100 mL), dried over
sodium sulfate, and concentrated *in-vacuo*. The residue
was purified over silica gel, eluting with 10% - 20%
ethyl acetate/heptane to yield 11.7 g of white solids as
product. NMR (500 MHz, DMSO) δ 9.54 (s, 1 H), 7.54 (d,
20 2H, J = 7 Hz), 7.23 (d, 2H, J = 8 Hz), 1.45 (s, 9H).
Yield = 88%.

Part B. Preparation of 2-tert-Butoxycarbonylamino-5-
25 trifluoromethoxy-benzoic acid.

A solution of (4-trifluoromethoxy-phenyl)-carbamic acid
tert-butyl ester (2.31 g, 8.33 mMol) in anhydrous THF (50
mL) at -78° C was treated with a 1.4 M solution of sec-
30 butyllithium in cyclohexane (13 mL, 18.33 mMol), at a
rate which did not allow the internal temperature to
exceed -60° C. The solution was stirred at -78° C for 15

minutes, then allowed to warm to -40° C and stirred for 2.5 hours. The reaction was treated with gaseous CO₂, stirred 30 minutes while warming to -20° C, then quenched with saturated ammonium chloride. The mixture was warmed
5 to room temperature, and extracted with ethyl acetate (3 x 50 mL). The combined organic phases were washed with water (50 mL), brine (50 mL), dried over sodium sulfate, and concentrated *in-vacuo*. The residue was triturated with hot heptane to yield 1.9 g of white powder as
10 product. NMR (500 MHz, DMSO) δ 12.89 (s, 1H), 8.24 (d, 1H, J = 9 Hz), 7.84 (s, 1H), 7.21 (d, 1H, J = 7 Hz), 1.51 (s, 9 Hz). Yield = 72%.

Part C. Preparation of 2-Amino-5-trifluoromethoxy-
15 benzoic acid, HCl salt.

2-tert-Butoxycarbonylamino-5-trifluoromethoxy-benzoic acid (1.9 g, 5.91 mMol) was dissolved in a 4 N HCl solution in dioxane (15 mL), and the resulting suspension
20 was stirred at room temperature for 6 hours. Analysis by LC/MS showed that the reaction was incomplete, so concentrated HCl (1 mL) was added, followed by methylene chloride (20 mL) to dissolve the solids, and the reaction was stirred overnight at room temperature. The mixture
25 was concentrated *in-vacuo*, then stripped from methanol (3 x 50 mL) to remove any excess HCl. The resulting solids were used as-is in the next step. MS (ES+) = 222 (M + H)⁺.

30

Part D. Preparation of 6-Trifluoromethoxy-quinazolin-4-
ol.

A mixture of 2-amino-5-trifluoromethoxy-benzoic acid, HCl salt (1.52 g, 5.91 mMol), and formamidine acetate (1.84 g, 17.73 mMol) in 2-ethoxyethanol (20 mL) was heated at reflux for 2 hours. Analysis by LC/MS showed that the reaction was complete, so the mixture was concentrated *in-vacuo*, and the residue was purified over silica gel, eluting with 50% ethyl acetate/heptane - 100% ethyl acetate, to yield 1.1 g of white solids as product. MS (ES+) = 231 (M + H)⁺. Yield = 82%.

Part E. Preparation of 4-Chloro-6-trifluoromethoxy-quinazoline.

The titled compound was prepared from 6-trifluoromethoxy-quinazolin-4-ol using the conditions described in example 137, part B. MS (ES+) = 249 (M + H)⁺.

Example 140 Part F. Preparation of 1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-(3S)-3-(6-trifluoromethoxy-pyrido[2,3-d]pyrimidin-4-ylamino)-pyrrolidin-2-one, TFA salt.

The titled compound was prepared from (3S)-3-amino-1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-pyrrolidin-2-one and of 4-chloro-6-trifluoromethoxy-quinazoline using the conditions described in example 106, part C. MS (ES+) = 620 (M + H)⁺.

Example 141

Preparation of 1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-cyclohexyl]-(3S)-3-(6-chloro-2-

methylamino-quinazolin-4-ylamino)-pyrrolidin-2-one, TFA salt

1-[(1S, 2R, 4R)-2-benzenesulfonylmethyl-4-(isopropyl-
 5 methyl-amino)-cyclohexyl]-(3S)-3-(2,6-dichloro-
 quinazolin-4-ylamino)-pyrrolidin-2-one (35 mg, 0.0487
 mmol, 1 eq.), 2.0 M mono-methylamine in THF (1.22 mL,
 2.44 mmol, 50 eq.), and THF (1 mL) were microwaved at 100
 °C until reaction was complete by LCMS. Purified by HPLC.
 10 Obtained 60 mg of white solids as product. LCMS detects
 (M+H)+ = 599.

Example 142

Preparation of (3S)-3-(6-Fluoro-quinazolin-4-ylamino)-1-
 15 [(1S, 2R, 4R)-4-(isopropyl-methyl-amino)-2-(toluene-4-
 sulfonylmethyl)-cyclohexyl]-pyrrolidin-2-one, TFA salt

Followed the procedure of Example 106 Part C starting
 from (3S)-3-amino-1-[(1S, 2R, 4R)-4-(isopropyl-methyl-
 20 amino)-2-(toluene-4-sulfonylmethyl)-cyclohexyl]-
 pyrrolidin-2-one (100c) and 4-chloro-6-fluoro-
 quinazoline. Purified by HPLC. LCMS detects (M+H)+ =
 568.

Example 143

Preparation of N-{1-[(1S, 2R, 4R)-2-
 benzenesulfonylmethyl-4-(isopropyl-methyl-amino)-
 cyclohexyl]-2-oxo-pyrrolidin-(3S)-3-yl}-2-chloro-5-
 25 trifluoromethyl-benzamide, TFA salt

30 Followed the procedure of Example 116 Part D starting
 from 2-chloro-5-trifluoromethyl-benzoic acid. Purified
 by HPLC. LCMS detects (M+H)+ = 614.

he next step: ESI MS m/z 507 $[C_{26}H_{29}F_3N_2O_3S + H]^+$.

Example 144

5 (S)-3-(6-Bromoquinazolin-4-ylamino)-1-((1S,2R,4R)-4-
 (isopropyl(methyl)amino)-2-
 (phenylsulfonylmethyl)cyclohexyl)pyrrolidin-2-one, TFA
 salt

10 (144a) 6-Bromo-4-chloroquinazoline was incorporated into
 Example 106, Part C give the title compound. MS found:
 $(M + H)^+ = 615$.

Example 145

15 (S)-3-(6,7-Difluoroquinazolin-4-ylamino)-1-((1S,2R,4R)-4-
 (isopropyl(methyl)amino)-2-
 (phenylsulfonylmethyl)cyclohexyl)pyrrolidin-2-one, TFA
 salt

20 (145a) 4-Chloro-6,7-difluoroquinazoline was incorporated
 into Example 106, Part C give the title compound. MS
 found: $(M + H)^+ = 572$.

Example 146

25 (S)-3-(6-Methoxyquinazolin-4-ylamino)-1-((1S,2R,4R)-4-
 (isopropyl(methyl)amino)-2-
 (phenylsulfonylmethyl)cyclohexyl)pyrrolidin-2-one, TFA
 salt

30 (146a) 4-Chloro-6-methoxyquinazoline was incorporated
 into Example 106, Part C give the title compound. MS
 found: $(M + H)^+ = 566$.

Example 147

((S)-1-((1S,2R,4R)-4-(isopropyl(methyl)amino)-2-(phenylsulfonylmethyl)cyclohexyl)-3-(quinazolin-4-ylamino)pyrrolidin-2-one, TFA salt

5

(147a) 4-Chloroquinazoline was incorporated into Example 106, Part C give the title compound. MS found: (M + H)⁺ = 536.

10

Example 148

3-Phenyl-N-((S)-1-((1S,2R,4R)-4-(isopropyl(methyl)amino)-2-(phenylsulfonylmethyl)cyclohexyl)-2-oxopyrrolidin-3-yl)benzamide, TFA salt

15

(148a) 3-Phenyl-benzoic acid was incorporated into Example 132 give the title compound. MS found: (M + H)⁺ = 588.

Example 149

20

(S)-3-(6-Iodoquinazolin-4-ylamino)-1-((1S,2R,4R)-4-(isopropyl(methyl)amino)-2-(phenylsulfonylmethyl)cyclohexyl)pyrrolidin-2-one, TFA salt

25

(149a) 4-Chloro-6-iodoquinazoline was incorporated into Example 106, Part C give the title compound. MS found: (M + H)⁺ = 662.

Example 150

30

3-Tert-butyl-4-hydroxy-N-((S)-1-((1S,2R,4R)-4-(isopropyl(methyl)amino)-2-(phenylsulfonylmethyl)cyclohexyl)-2-oxopyrrolidin-3-yl)benzamide, TFA salt

(150a) 3-Tert-butyl-4-hydroxybenzoic acid was incorporated into Example 132 give the title compound. MS found: $(M + H)^+ = 584$.

5

Example 151

3-Amino-5-tert-butyl-N-((S)-1-((1S,2R,4R)-4-(isopropyl(methyl)amino)-2-(phenylsulfonylmethyl)cyclohexyl)-2-oxopyrrolidin-3-yl)thiophene-2-carboxamide, TFA salt

10

(151a) 3-Amino-5-tert-butylthiophene-2-carboxylic acid was incorporated into Example 132 give the title compound. MS found: $(M + H)^+ = 589$.

15

Example 152

N-((S)-1-((1S,2R,4R)-4-(Isopropyl(methyl)amino)-2-(phenylsulfonylmethyl)cyclohexyl)-2-oxopyrrolidin-3-yl)-2-methyl-5-phenylfuran-3-carboxamide, TFA salt

20

(152a) 2-Methyl-5-phenylfuran-3-carboxylic acid was incorporated into Example 132 give the title compound. MS found: $(M + H)^+ = 592$.

25

Example 153

N-((S)-1-((1S,2R,4R)-4-(Isopropyl(methyl)amino)-2-(phenylsulfonylmethyl)cyclohexyl)-2-oxopyrrolidin-3-yl)-5-nitrofuran-2-carboxamide, TFA salt

30 (153a) 5-Nitrofuran-2-carboxylic acid was incorporated into Example 132 give the title compound. MS found: $(M + H)^+ = 547$.

Example 154

N-((S)-1-((1S,2R,4R)-4-(Isopropyl(methyl)amino)-2-(phenylsulfonylmethyl)cyclohexyl)-2-oxopyrrolidin-3-yl)-4-phenylthiophene-2-carboxamide, TFA salt

5

(154a) 4-Phenylthiophene-2-carboxylic acid was incorporated into Example 132 give the title compound.

MS found: (M + H)⁺ = 594.

10

Example 155

N-((S)-2-Oxo-1-((1S,2R,4R)-2-(phenylsulfonylmethyl)-4-(pyrrolidin-1-yl)cyclohexyl)pyrrolidin-3-yl)-3-(trifluoromethyl)benzamide, TFA salt

15

(155a) Tert-butyl (S)-1-((1S,2R,4R)-4-amino-2-(phenylsulfonylmethyl)cyclohexyl)-2-oxopyrrolidin-3-ylcarbamate (52c) (80 mg) was dissolved in DMF prior to the addition 1,4-dibromobutane and K₂CO₃ (75 mg). After 16 h, water and EtOAc were added. The organic layer was dried, filtered, and concentrated. The resulting residue was dissolved in CH₂Cl₂ (2 mL) and cooled to 0 °C prior to the addition of TFA (2 mL). After the reaction was warmed to rt over 1 h, it was concentrated and dried. This material was dissolved in DMF prior to the addition of (iPr)₂NEt (0.03 mL) and 3-trifluoromethylbenzoic acid (33 mg). After cooling to 0 °C, HATU (78 mg) was added. The resulting mixture was warmed to rt and was stirred overnight. The solution was diluted with EtOAc and was washed with sat. NaHCO₃. The organic phase was dried (MgSO₄), filtered, and concentrated. Reverse phase HPLC purification (gradient elution, water/acetonitrile/TFA)

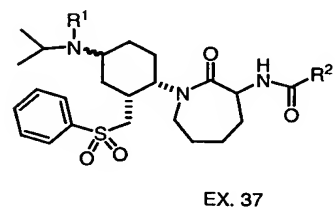
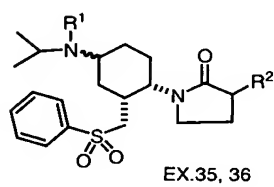
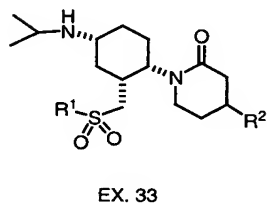
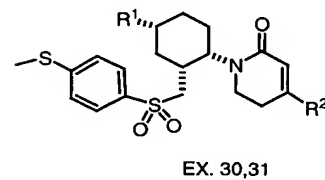
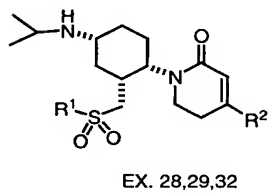
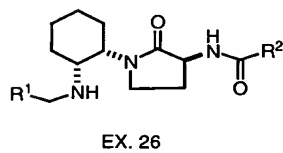
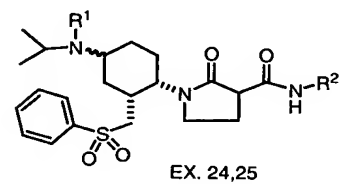
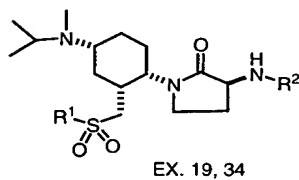
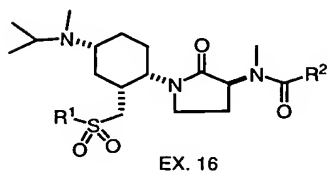
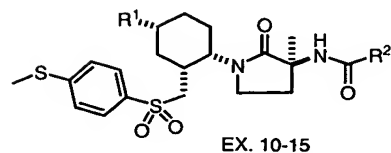
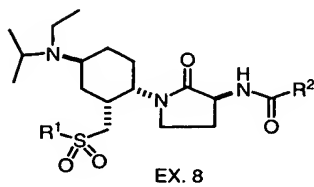
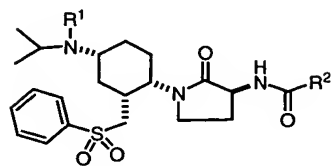
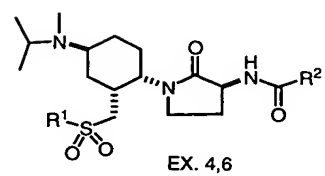
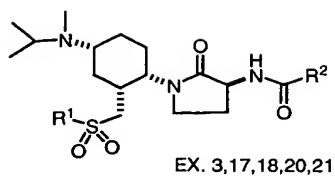
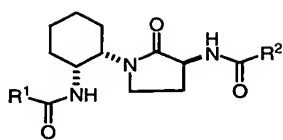
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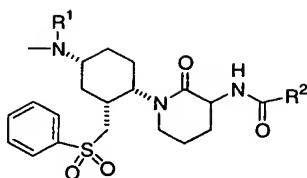
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of the resulting residue provided the title compound (5 mg). MS found: $(M+H)^+ = 578.3$.

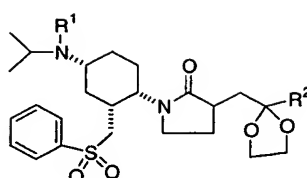
Table 1 contains representative examples of the present invention. Each of the following structural formulas are to be used in the indicated example (Ex) range paired with the given R¹ and R² substituent. The R¹ and R² described in the tables may be the same or different than those described in the claims

Table 1

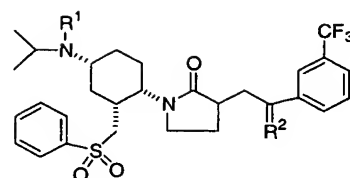




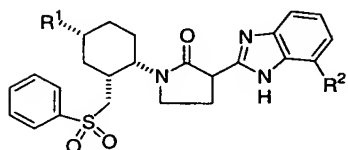
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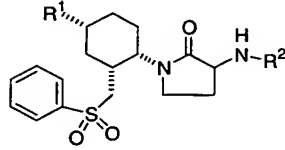
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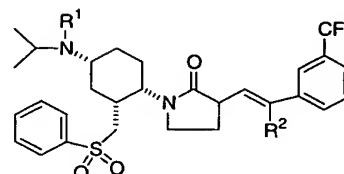
Ex. 41, 42, 45, 46



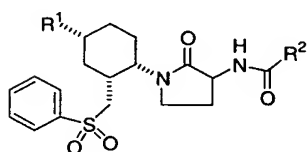
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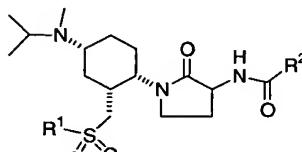
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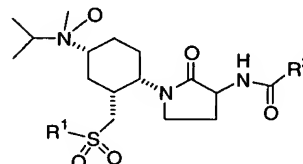
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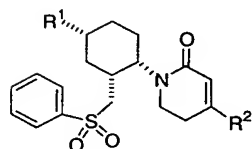
Ex. 61, 62, 73-84, 155



Ex. 85-92, 97-101



Ex. 93-96



Ex. 102-105

Ex	R ¹	R ²	MS [M+H]
1	4-(methylthio)phenyl	2-(t-butoxycarbonyl)amino-5-trifluoromethylphenyl	635.4 M+H
2	4-(methylthio)phenyl	2-amino-5-trifluoromethylphenyl	535.4 M+H
3	4-methylphenyl	3-trifluoromethylphenyl	594.3
4	4-methylphenyl	3-trifluoromethylphenyl	594.3
5	methyl	3-trifluoromethylphenyl	580.3
6	phenyl	3-trifluoromethylphenyl	580.3

7	ethyl	3-trifluoromethylphenyl	594.3
8	phenyl	3-trifluoromethylphenyl	594.3
9	cyclopropylmethyl	3-trifluoromethylphenyl	620.3
10	azido	3-trifluoromethylphenyl	610.5
11	amino	3-trifluoromethylphenyl	584.5
12	isopropylamino	3-trifluoromethylphenyl	626.6
13	isopropyl(methyl)amino	3-trifluoromethylphenyl	640.6
14	isopropyl(propargyl)amino	3-trifluoromethylphenyl	664.6
15	isopropyl(cyclopropylmethyl)amino	3-trifluoromethylphenyl	680.6
16	4-(methylthio)phenyl	3-trifluoromethylphenyl	640.3
17	4-(methylthio)phenyl	3-trifluoromethylphenyl	626.3
18	4-(methylthio)phenyl	3-(trifluoromethyl)phenyl amino	641.3
19	4-(methylthio)phenyl	3-(trifluoromethyl)phenyl sulfonyl	662.3
20	4-(methylthio)phenyl	phenyl	558.3
21	phenyl	3-(trifluoromethyl)phenyl amino	595.3
22	H	3-trifluoromethylphenyl	566.4
23	allyl	3-trifluoromethylphenyl	606.3
24	H	3-trifluoromethylphenyl	566.3
25	H	3-trifluoromethylphenyl	566.5
26	4-(methylthio)phenyl	2-(t-butoxycarbonyl)amino-5-trifluoromethylphenyl	621.4
27	propyl	3-trifluoromethylphenyl	608.3
28	4-(methylthio)phenyl	3-trifluoromethylphenyl	581

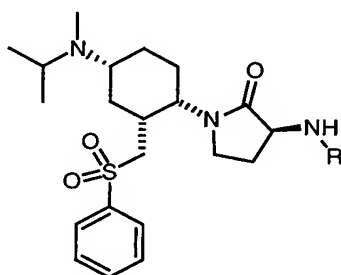
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30	isopropyl(methyl)amino	3-trifluoromethylphenyl	595.4
31	amino	3-trifluoromethoxyphenyl	555.2
32	4-(methylthio)phenyl	3-trifluoromethoxyphenyl	597.2
33	4-(methylthio)phenyl	3-trifluoromethylphenyl	537
34	4-(methylthio)phenyl	3-(trifluoromethyl)phenyl methylene	612.3
35	H	3-(trifluoromethyl)phenyl ethylene	NMR
36	H	3-(trifluoromethyl)phenyl ethylene	551.4
37	methyl	3-trifluoromethylphenyl	608
38	methyl	3-trifluoromethylphenyl	566
39	methyl	3-trifluoromethylphenyl	623
40	methyl	3-trifluoromethylphenyl	623
41	methyl	O	579
42	methyl	O	579
43	methyl	OH	581
44	methyl	OH	581
45	methyl	methoxyamino	608
46	methyl	methoxyamino	608
47	amino	trifluoromethyl	521
48	isopropylamino	trifluoromethyl	563
49	isopropyl(methyl)amino	trifluoromethyl	577
50	isopropyl(ethyl)amino	trifluoromethyl	591
51	diethylamino	trifluoromethyl	577
52	isopropyl(methyl)amino	1-naphthalenyl	534

53	isopropyl (methyl) amino	3-benzo[b]thiophenyl	540
54	isopropyl (methyl) amino	6-chloroquinazolin-4-yl	570.2
55	isopropyl (methyl) amino	6,8-dichloroquinazolin-4-yl	604.2
56	methyl	3,5-dichlorophenyl	580
57	methyl	3-trifluoromethoxyphenyl	596.2
58	methyl	H	563
59	methyl	methyl	577
60	methyl	phenyl	512
61	isopropyl (methyl) amino	3,5-bis-trifluoromethylphenyl	648
62	isopropyl (methyl) amino	2-amino-5-trifluoromethoxyphenyl	611
63	isopropyl (methyl) amino	6-trifluoromethylquinolin-4-yl	603.2
64	isopropyl (methyl) amino	6-trifluoromethylquinolin-4-yl	603.2
65	isopropyl (methyl) amino	7-trifluoromethylquinolin-4-yl	603.2
66	isopropyl (methyl) amino	7-trifluoromethylquinolin-4-yl	603.2
67	isopropyl (methyl) amino	2-phenyl-phenyl	560.3
68	isopropyl (methyl) amino	3,5-bis-trifluoromethylphenyl	620.2
69	isopropyl (methyl) amino	2-trifluoromethylphenyl	552.3
70	isopropyl (methyl) amino	2-trifluoromethoxyphenyl	568.3

71	isopropyl (methyl) amino	3-trifluoromethylphenyl	552.3
72	isopropyl (methyl) amino	4-trifluoromethylphenyl	552.3
73	isopropyl (methyl) amino	3-chlorophenyl	546
74	isopropyl (methyl) amino	3-fluoro-5-trifluoromethylphenyl	648
75	t-butoxycarbonylamino	3-trifluoromethylphenyl	624.7
76	phenyl	3-trifluoromethylphenyl	600.1
77	pyridin-3-yl	3-trifluoromethylphenyl	601
78	thiazolin-2-yl	3-trifluoromethylphenyl	607
79	methoxycarbonylamino	3-trifluoromethylphenyl	582.2
80	formamidyl	3-trifluoromethylphenyl	552.3
81	aminocarbonylamino	3-trifluoromethylphenyl	567.3
82	(methylamino) carbonyl amino	3-trifluoromethylphenyl	581.3
83	2-oxo-pyrrolidin-1-yl	3-trifluoromethylphenyl	592
84	1,1-dioxido-isothiazolidin-2-yl	3-trifluoromethylphenyl	628
85	4-chlorophenyl	3-fluoro-5-trifluoromethylphenyl	632
86	4-chlorophenyl	3-chlorophenyl	580
87	4-chlorophenyl	3,5-bis-trifluoromethylphenyl	683
88	4-chlorophenyl	2-tert-butoxycarbonylamino-5-trifluoromethoxyphenyl	746
89	4-chlorophenyl	2-amino-5-trifluoromethoxyphenyl	645
90	4-chlorophenyl	3-trifluoromethoxyphenyl	630.2
91	4-chlorophenyl	3-trifluoromethylphenyl	614.0
92	4-chlorophenyl	3,5-bis-chloro-phenyl	614.2
93	4-chlorophenyl	3-chlorophenyl	596

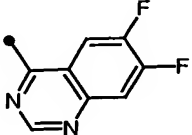
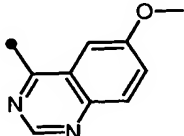
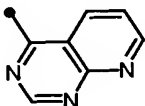
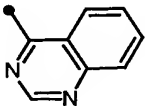
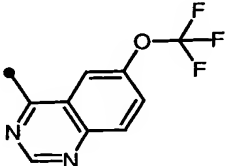
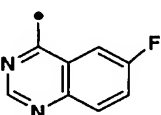
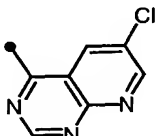
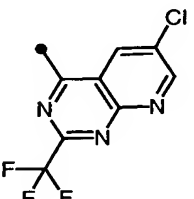
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95	4-chlorophenyl	3-fluoro-5-trifluoromethylphenyl	649.1
96	phenyl	3-trifluoromethylphenyl	596.3
97	4-isopropyl-phenyl	3-trifluoromethylphenyl	622.3
98	2-methyl-phenyl	3-trifluoromethylphenyl	594.6
99	4-fluoro-phenyl	3-trifluoromethylphenyl	598.5
100	4-methyl-phenyl	3-chloro-phenyl	560.2
101	4-methyl-phenyl	2-amino-5-trifluoromethoxyphenyl	625.2
102	amino	3-trifluoromethylphenyl	493.4
103	isopropylamino	3-trifluoromethylphenyl	535.2
104	isopropyl (methyl) amino	3-trifluoromethylphenyl	548.7
105	isopropyl (ethyl) amino	3-trifluoromethylphenyl	563.3
155	pyrrolidin-1-yl	3-trifluoromethylphenyl	578.3

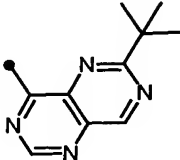
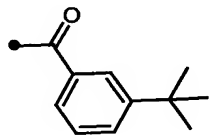
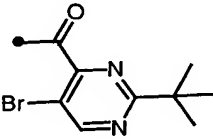
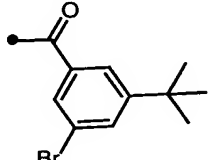
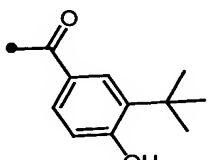
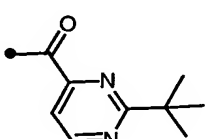
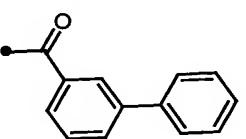
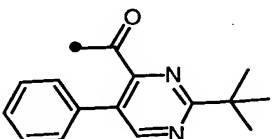
Table A

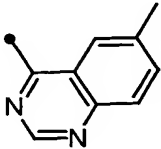
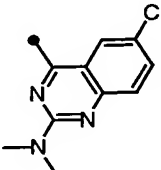
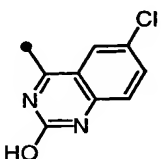
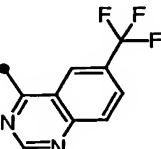
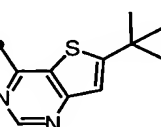
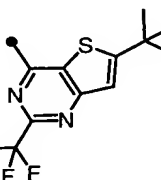
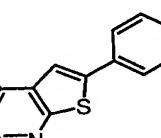
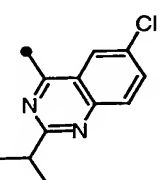


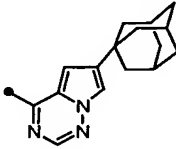
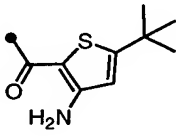
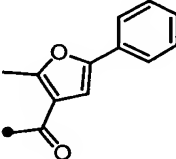
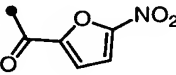
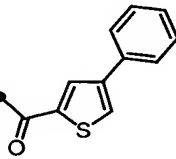
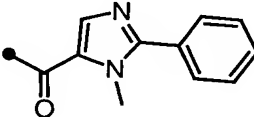
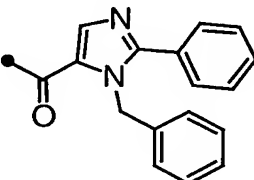
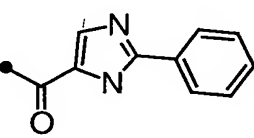
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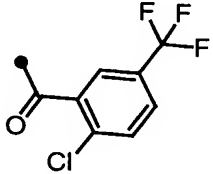
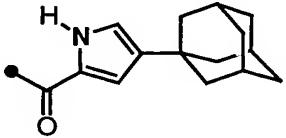
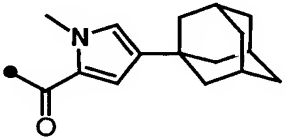
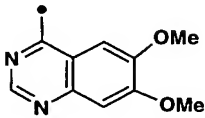
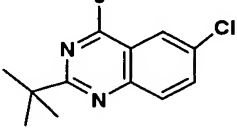
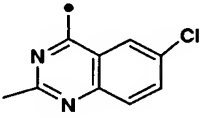
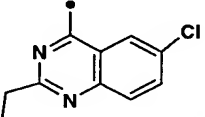
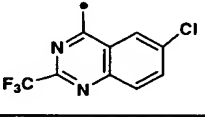
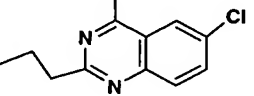
No.	R	MS
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145	 <chem>Fc1cc2ncnc2cc1I</chem>	572
146	 <chem>COc1cc2ncnc2cc1I</chem>	566
137	 <chem>Ic1ccc2ncnc2c1</chem>	537
147	 <chem>Ic1ccc2c(c1)ncn2</chem>	536
140	 <chem>COc1cc2ncnc2cc1I(F)(F)F</chem>	620
120	 <chem>Fc1cc2ncnc2cc1I</chem>	554
138	 <chem>Clc1cc2ncnc2cc1I</chem>	572
139	 <chem>Clc1cc2nc3c(ncn3cc2I)C(F)(F)F</chem>	639

131	 <chem>CC1=NC2=NC=NC=C2N1C(C)(C)C</chem>	594
135	 <chem>CC(C)(C)c1ccc(cc1)C(=O)O</chem>	568
132	 <chem>CC(C)(C)C1=NC2=CC(=C(N2)C(=O)O)N1Br</chem>	648
136	 <chem>CC(C)(C)c1cc(Br)ccc1C(=O)O</chem>	647
150	 <chem>CC(C)(C)c1ccc(O)cc1C(=O)O</chem>	584
133	 <chem>CC(C)(C)C1=NC2=CC(=C(N2)C(=O)O)N1</chem>	570
148	 <chem>c1ccc(cc1)-c2ccccc2C(=O)O</chem>	588
134	 <chem>CC(C)(C)C1=NC2=CC(=C(N2)C(=O)O)N1c3ccccc3</chem>	646

121	 <chem>Cc1ccc2ncnc2c1</chem>	550
109	 <chem>CN(C)c1nc2cc(Cl)ccc2n1</chem>	613
110	 <chem>O=C(O)c1nc2cc(Cl)ccc2n1</chem>	586
111	 <chem>FC(F)(F)c1ccc2ncnc2c1</chem>	604
112	 <chem>CC(C)(C)c1cc2ncnc2s1</chem>	598
113	 <chem>CC(C)(C)c1cc2nc(C(F)(F)F)n2s1</chem>	666
122	 <chem>c1ccccc1c2cc3ncnc3s2</chem>	618
124	 <chem>CC(C)c1nc2cc(Cl)ccc2n1</chem>	612

115		659
151		589
152		592
153		547
154		594
116		592
117		668
118		577

143	 <chem>CC(=O)c1cc(C(F)(F)F)c(Cl)cc1</chem>	614
129	 <chem>NC(=O)c1cc(C23CC4CC(CC(C4)C2)CC3)n[nH]1</chem>	636
130	 <chem>CC1=CN(C(=O)N)C=C1C23CC4CC(CC(C4)C2)CC3</chem>	649
119	 <chem>COC1=CC=C2N=CN(C2=O)N1</chem>	596
125	 <chem>CC(C)(C)C1=NC2=CC=C(Cl)C=C2N1=O</chem>	626
126	 <chem>C1=NC2=CC=C(Cl)C=C2N1=O</chem>	585
127	 <chem>CC1=NC2=CC=C(Cl)C=C2N1=O</chem>	599
106	 <chem>Fc1cc2cc(Cl)ccc2n1</chem>	638
123	 <chem>CCC1=NC2=CC=C(Cl)C=C2N1=O</chem>	613

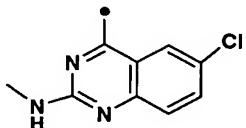
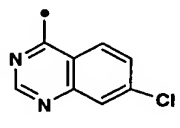
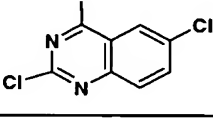
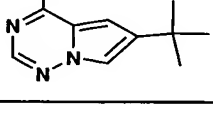
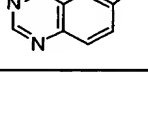
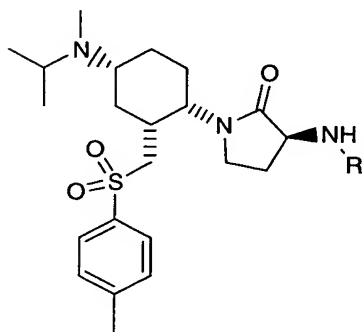
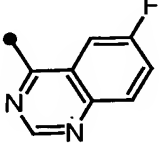
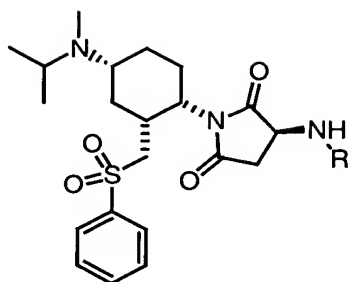
141		599
107		570
108		604
114		581
149		662

Table B



142		568
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128		594
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5

UTILITY

Compounds of formula I are shown to be modulators of chemokine receptor activity using assays known by those skilled in the art. In this section, we describe these assays and give their literature reference. By displaying activity in these assays of MCP-1 antagonism, compounds of formula I are expected to be useful in the treatment of human diseases associated with chemokines and their cognate receptors. The definition of activity in these assays is a compound demonstrating an IC_{50} of 20 μM or lower in concentration when measured in a particular assay.

Antagonism of MCP-1 Binding to Human PBMC

(Yoshimura et al., *J. Immunol.* 1990, 145, 292)

Compounds of the present invention have activity in the antagonism of MCP-1 binding to human PBMC (human peripheral blood mononuclear cells) described here.

Millipore filter plates (#MABVN1250) are treated with 100 μ l of binding buffer (0.5% bovine serum albumin, 20 mM HEPES buffer and 5 mM magnesium chloride in RPMI 1640 media) for thirty minutes at room temperature. To
5 measure binding, 50 μ l of binding buffer, with or without a known concentration compound, is combined with 50 μ l of 125 -I labeled human MCP-1 (to give a final concentration of 150 pM radioligand) and 50 μ l of binding buffer containing 5×10^5 cells. Cells used for such binding
10 assays can include human peripheral blood mononuclear cells isolated by Ficoll-Hypaque gradient centrifugation, human monocytes (Weiner et al., *J. Immunol. Methods*. **1980**, 36, 89), or the THP-1 cell line which expresses the endogenous receptor. The mixture of compound, cells and
15 radioligand are incubated at room temperature for thirty minutes. Plates are placed onto a vacuum manifold, vacuum applied, and the plates washed three times with binding buffer containing 0.5M NaCl. The plastic skirt is removed from the plate, the plate allowed to air dry,
20 the wells punched out and counted. The percent inhibition of binding is calculated using the total counts obtained in the absence of any competing compound and the background binding determined by addition of 100 nM MCP-1 in place of the test compound.

25

Antagonism of MCP-1-induced Calcium Influx

(Sullivan, et al. *Methods Mol. Biol.*, 114, 125-133 (1999))

Compounds of the present invention have activity in the antagonism of MCP-1-induced calcium influx assay
30 described here.

Calcium mobilization is measured using the fluorescent Ca^{2+} indicator dye, Fluo-3. Cells are

incubated at 8×10^5 cells/ml in phosphate-buffered saline containing 0.1% bovine serum albumin, 20 mM HEPES buffer, 5 mM glucose, 1% fetal bovine serum, 4 μ M Fluo-3 AM and 2.5 mM probenecid for 60 minutes at 37°C. Cells
5 used for such calcium assays can include human monocytes isolated as described by Weiner et al., J. Immunol. Methods, 36, 89-97 (1980) or cell lines which expresses the endogenous CCR2 receptor such as THP-1 and MonoMac-6. The cells are then washed three times in phosphate-
10 buffered saline containing 0.1% bovine serum albumin, 20 mM HEPES, 5 mM glucose and 2.5 mM probenecid. The cells are resuspended in phosphate-buffered saline containing 0.5% bovine serum albumin, 20 mM HEPES and 2.5 mM probenecid at a final concentration of $2-4 \times 10^6$
15 cells/ml. Cells are plated into 96-well, black-wall microplates (100 μ l/well) and the plates centrifuged at 200 x g for 5 minutes. Various concentrations of compound are added to the wells (50 μ l/well) and after 5 minutes, 50 μ l/well of MCP-1 is added to give a final
20 concentration of 10 nM. Calcium mobilization is detected by using a fluorescent-imaging plate reader. The cell monolayer is excited with an argon laser (488 nm) and cell-associated fluorescence measured for 3 minutes, (every second for the first 90 seconds and every 10
25 seconds for the next 90 seconds). Data are generated as arbitrary fluorescence units and the change in fluorescence for each well determined as the maximum-minimum differential. Compound-dependent inhibition is calculated relative to the response of MCP-1 alone.

30

Antagonism of MCP-1-induced Human PBMC Chemotaxis

(Bacon et al., *Brit. J. Pharmacol.* **1988**, 95, 966)

Compounds of the present invention have activity in the antagonism of MCP-1-induced human PBMC chemotaxis assay described here.

Neuroprobe MBA96-96-well chemotaxis chamber,
5 Polyfiltronics MPC 96 well plate, and Neuroprobe polyvinylpyrrolidone-free polycarbonate PFD5 8-micron filters are warmed in a 37 °C incubator. Human Peripheral Blood Mononuclear Cells (PBMCs) (Boyum et al., *Scand. J. Clin. Lab Invest. Suppl.* **1968**, 97, 31), freshly isolated
10 via the standard ficoll density separation method, are suspended in DMEM at 1×10^7 c/ml and warmed at 37°C. A 60nM solution of human MCP-1 is also warmed at 37°C. Dilutions of test compounds are made up at 2x the concentration needed in DMEM. The PBMC suspension and
15 the 60nm MCP-1 solution are mixed 1:1 in polypropylene tubes with prewarmed DMEM with or without a dilution of the test compounds. These mixtures are warmed in a 37°C tube warmer. To start the assay, add the MCP-1/compound mixture into the wells of the Polyfiltronics MPC 96 well
20 plate that has been placed into the bottom part of the Neuroprobe chemotaxis chamber. The approximate volume is 400µl to each well and there should be a positive meniscus after dispensing. The 8 micron filter is placed gently on top of the 96 well plate, a rubber gasket is
25 attached to the bottom of the upper chamber, and the chamber is assembled. A 200µl volume of the cell suspension/compound mixture is added to the appropriate wells of the upper chamber. The upper chamber is covered with a plate sealer, and the assembled unit is placed in
30 a 37°C incubator for 45 minutes. After incubation, the plate sealer is removed and all the remaining cell suspension is aspirated off. The chamber is disassembled

and the filter gently removed. While holding the filter at a 90 degree angle, unmigrated cells are washed away using a gentle stream of phosphate buffered saline and the top of the filter wiped with the tip of a rubber
5 squeegee. Repeat this wash twice more. The filter is air dried and then immersed completely in Wright Geimsa stain for 45 seconds. The filter is then washed by soaking in distilled water for 7 minutes, and then a 15 second additional wash in fresh distilled water. The
10 filter is again air dried. Migrated cells on the filter are quantified by visual microscopy.

Mammalian chemokine receptors provide a target for interfering with or promoting immune cell function in a mammal, such as a human. Compounds that inhibit or
15 promote chemokine receptor function are particularly useful for modulating immune cell function for therapeutic purposes. Accordingly, the present invention is directed to compounds which are useful in the prevention and/or treatment of a wide variety of
20 inflammatory, infectious, and immunoregulatory disorders and diseases, including asthma and allergic diseases, infection by pathogenic microbes (which, by definition, includes viruses), as well as autoimmune pathologies such as the rheumatoid arthritis and atherosclerosis.

For example, an instant compound which inhibits one or more functions of a mammalian chemokine receptor (e.g., a human chemokine receptor) may be administered to inhibit (i.e., reduce or prevent) inflammation or
25 infectious disease. As a result, one or more inflammatory process, such as leukocyte emigration, adhesion, chemotaxis, exocytosis (e.g., of enzymes, histamine) or inflammatory mediator release, is
30 inhibited.

Similarly, an instant compound which promotes one or more functions of the mammalian chemokine receptor (e.g., a human chemokine) as administered to stimulate (induce or enhance) an immune or inflammatory response, such as leukocyte emigration, adhesion, chemotaxis, exocytosis (e.g., of enzymes, histamine) or inflammatory mediator release, resulting in the beneficial stimulation of inflammatory processes. For example, eosinophils can be recruited to combat parasitic infections. In addition, treatment of the aforementioned inflammatory, allergic and autoimmune diseases can also be contemplated for an instant compound which promotes one or more functions of the mammalian chemokine receptor if one contemplates the delivery of sufficient compound to cause the loss of receptor expression on cells through the induction of chemokine receptor internalization or the delivery of compound in a manner that results in the misdirection of the migration of cells.

In addition to primates, such as humans, a variety of other mammals can be treated according to the method of the present invention. For instance, mammals, including but not limited to, cows, sheep, goats, horses, dogs, cats, guinea pigs, rats or other bovine, ovine, equine, canine, feline, rodent or murine species can be treated. However, the method can also be practiced in other species, such as avian species. The subject treated in the methods above is a mammal, male or female, in whom modulation of chemokine receptor activity is desired. "Modulation" as used herein is intended to encompass antagonism, agonism; partial antagonism and/or partial agonism.

Diseases or conditions of human or other species which can be treated with inhibitors of chemokine

receptor function, include, but are not limited to:
inflammatory or allergic diseases and conditions,
including respiratory allergic diseases such as asthma,
allergic rhinitis, hypersensitivity lung diseases,
5 hypersensitivity pneumonitis, eosinophilic cellulitis
(e.g., Wells's syndrome), eosinophilic pneumonias (e.g.,
Loeffler's syndrome, chronic eosinophilic pneumonia),
eosinophilic fasciitis (e.g., Shulman's syndrome),
delayed-type hypersensitivity, interstitial lung diseases
10 (ILD) (e.g., idiopathic pulmonary fibrosis, or ILD
associated with rheumatoid arthritis, systemic lupus
erythematosus, ankylosing spondylitis, systemic
sclerosis, Sjogren's syndrome, polymyositis or
dermatomyositis); systemic anaphylaxis or
15 hypersensitivity responses, drug allergies (e.g., to
penicillin, cephalosporins), eosinophilia-myalgia
syndrome due to the ingestion of contaminated tryptophan,
insect sting allergies; autoimmune diseases, such as
rheumatoid arthritis, psoriatic arthritis, multiple
20 sclerosis, systemic lupus erythematosus, myasthenia
gravis, juvenile onset diabetes; glomerulonephritis,
autoimmune thyroiditis, Behcet's disease; graft rejection
(e.g., in transplantation), including allograft rejection
or graft-versus-host disease; inflammatory bowel
25 diseases, such as Crohn's disease and ulcerative colitis;
spondyloarthropathies; scleroderma; psoriasis (including
T-cell mediated psoriasis) and inflammatory dermatoses
such as an dermatitis, eczema, atopic dermatitis,
allergic contact dermatitis, urticaria; vasculitis (e.g.,
30 necrotizing, cutaneous, and hypersensitivity vasculitis);
eosinophilic myositis, eosinophilic fasciitis; cancers
with leukocyte infiltration of the skin or organs. Other
diseases or conditions in which undesirable inflammatory

responses are to be inhibited can be treated, including, but not limited to, reperfusion injury, atherosclerosis, certain hematologic malignancies, cytokine-induced toxicity (e.g., septic shock, endotoxic shock),

5 polymyositis, dermatomyositis. Infectious diseases or conditions of human or other species which can be treated with inhibitors of chemokine receptor function, include, but are not limited to, HIV.

Diseases or conditions of humans or other species
10 which can be treated with promoters of chemokine receptor function, include, but are not limited to:
immunosuppression, such as that in individuals with immunodeficiency syndromes such as AIDS or other viral infections, individuals undergoing radiation therapy,
15 chemotherapy, therapy for autoimmune disease or drug therapy (e.g., corticosteroid therapy), which causes immunosuppression; immunosuppression due to congenital deficiency in receptor function or other causes; and infections diseases, such as parasitic diseases,
20 including, but not limited to helminth infections, such as nematodes (round worms); (Trichuriasis, Enterobiasis, Ascariasis, Hookworm, Strongyloidiasis, Trichinosis, filariasis); trematodes (flukes) (Schistosomiasis, Clonorchiasis), cestodes (tape worms) (Echinococcosis, Taeniasis saginata, Cysticercosis); visceral worms,
25 visceral larva migraines (e.g., Toxocara), eosinophilic gastroenteritis (e.g., Anisaki sp., Phocanema sp.), cutaneous larva migraines (Ancylostoma braziliense, Ancylostoma caninum). The compounds of the present
30 invention are accordingly useful in the prevention and treatment of a wide variety of inflammatory, infectious and immunoregulatory disorders and diseases.

In addition, treatment of the aforementioned inflammatory, allergic and autoimmune diseases can also be contemplated for promoters of chemokine receptor function if one contemplates the delivery of sufficient
5 compound to cause the loss of receptor expression on cells through the induction of chemokine receptor internalization or delivery of compound in a manner that results in the misdirection of the migration of cells.

In another aspect, the instant invention may be used
10 to evaluate the putative specific agonists or antagonists of a G protein coupled receptor. The present invention is directed to the use of these compounds in the preparation and execution of screening assays for compounds that modulate the activity of chemokine
15 receptors. Furthermore, the compounds of this invention are useful in establishing or determining the binding site of other compounds to chemokine receptors, e.g., by competitive inhibition or as a reference in an assay to compare its known activity to a compound with an unknown
20 activity. When developing new assays or protocols, compounds according to the present invention could be used to test their effectiveness. Specifically, such compounds may be provided in a commercial kit, for example, for use in pharmaceutical research involving the
25 aforementioned diseases. The compounds of the instant invention are also useful for the evaluation of putative specific modulators of the chemokine receptors. In addition, one could utilize compounds of this invention to examine the specificity of G protein coupled receptors
30 that are not thought to be chemokine receptors, either by serving as examples of compounds which do not bind or as structural variants of compounds active on these

receptors which may help define specific sites of interaction.

The compounds of the present invention are used to treat or prevent disorders selected from rheumatoid
5 arthritis, osteoarthritis, septic shock, atherosclerosis, aneurism, fever, cardiovascular effects, haemodynamic shock, sepsis syndrom, post ischemic reperfusion injury, malaria, Crohn's disease, inflammatory bowel diseases, mycobacterial infection, meningitis, psoriasis,
10 congestive heart failure, fibrotic diseases, cachexia, graft rejection, autoimmune diseases, skin inflammatory diseases, multiple sclerosis, radiation damage, hyperoxic alveolar injury, HIV, HIV dementia, non-insulin dependent diabetes melitus, asthma, allergic rhinitis, atopic
15 dermatitis, idiopathic pulmonary fibrosis, bullous pemphigoid, helminthic parasitic infections, allergic colitis, eczema, conjunctivitis, transplantation, familial eosinophilia, eosinophilic cellulitis, eosinophilic pneumonias, eosinophilic fasciitis,
20 eosinophilic gastroenteritis, drug induced eosinophilia, cystic fibrosis, Churg-Strauss syndrome, lymphoma, Hodgkin's disease, colonic carcinoma, Felty's syndrome, sarcoidosis, uveitis, Alzheimer, Glomerulonephritis, and systemic lupus erythematosus.

25 In another aspect, the compounds are used to treat or prevent inflammatory disorders selected from from rheumatoid arthritis, osteoarthritis, atherosclerosis, aneurism, fever, cardiovascular effects, Crohn's disease, inflammatory bowel diseases, psoriasis, congestive heart
30 failure, multiple sclerosis, autoimmune diseases, skin inflammatory diseases.

In another aspect, the compounds are used to treat or prevent inflammatory disorders selected from

rheumatoid arthritis, osteoarthritis, atherosclerosis, Crohn's disease, inflammatory bowel diseases, and multiple sclerosis.

Combined therapy to prevent and treat inflammatory,
5 infectious and immunoregulatory disorders and diseases, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis, and those pathologies noted above is illustrated by the combination of the compounds of this
10 invention and other compounds which are known for such utilities. For example, in the treatment or prevention of inflammation, the present compounds may be used in conjunction with an anti-inflammatory or analgesic agent such as an opiate agonist, a lipoxygenase inhibitor, a
15 cyclooxygenase-2 inhibitor, an interleukin inhibitor, such as an interleukin-1 inhibitor, a tumor necrosis factor inhibitor, an NMDA antagonist, an inhibitor of nitric oxide or an inhibitor of the synthesis of nitric oxide, a non-steroidal anti-inflammatory agent, a
20 phosphodiesterase inhibitor, or a cytokine-suppressing anti-inflammatory agent, for example with a compound such as acetaminophen, aspirin, codeine, fentanyl, ibuprofen, indomethacin, ketorolac, morphine, naproxen, phenacetin, piroxicam, a steroidal analgesic, sufentanyl, sunlindac,
25 interferon alpha and the like. Similarly, the instant compounds may be administered with a pain reliever; a potentiator such as caffeine, an H₂-antagonist, simethicone, aluminum or magnesium hydroxide; a decongestant such as phenylephrine, phenylpropanolamine,
30 pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levodesoxy-ephedrine; and antitussive such as codeine, hydrocodone, caramiphen, carbetapentane, or dextramethorphan; a diuretic; and a

sedating or non-sedating antihistamine. Likewise, compounds of the present invention may be used in combination with other drugs that are used in the treatment/prevention/suppression or amelioration of the diseases or conditions for which compound of the present invention are useful. Such other drugs may be administered, by a route and in an amount commonly used therefore, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the present invention may be used. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of the present invention.

Examples of other active ingredients that may be combined with a compound of the present invention, either administered separately or in the same pharmaceutical compositions, include, but are not limited to: (a) integrin antagonists such as those for selectins, ICAMs and VLA-4; (b) steroids such as beclomethasone, methylprednisolone, betamethasone, prednisone, dexamethasone, and hydrocortisone; (c) immunosuppressants such as cyclosporin, tacrolimus, rapamycin and other FK-506 type immunosuppressants; (d) antihistamines (H1-histamine antagonists) such as bromopheniramine, chlorpheniramine, dexchlorpheniramine, triprolidine, clemastine, diphenhydramine, diphenylpyraline, tripeleminamine, hydroxyzine, methdilazine, promethazine, trimeprazine, azatadine, cyproheptadine, antazoline, pheniramine pyrilamine, astemizole, terfenadine,

loratadine, cetirizine, fexofenadine, descarboethoxyloratadine, and the like; (e) non-steroidal anti-asthmatics such as b2-agonists (terbutaline, metaproterenol, fenoterol, isoetharine, albuteral, bitolterol, and pirbuterol), theophylline, cromolyn sodium, atropine, ipratropium bromide, leukotriene antagonists (zafirlukast, montelukast, pranlukast, iralukast, pobilukast, SKB-102,203), leukotriene biosynthesis inhibitors (zileuton, BAY-1005); (f) non-steroidal antiinflammatory agents (NSAIDs) such as propionic acid derivatives (alminoprofen, benxaprofen, bucloxic acid, carprofen, fenbufen, fenoprofen, fluprofen, flurbiprofen, ibuprofen, indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin, piroprofen, pranoprofen, suprofen, tiaprofenic acid, and tioxaprofen), acetic acid derivatives (indomethacin, acemetacin, alclofenac, clidanac, diclofenac, fenclofenac, fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, oxpinac, sulindac, tiopinac, tolmetin, zidometacin, and zomepirac), fenamic acid derivatives (flufenamic acid, meclofenamic acid, mefenamic acid, niflumic acid and tolfenamic acid), biphenylcarboxylic acid derivatives (diflunisal and flufenisal), oxicams (isoxicam, piroxicam, sudoxicam and tenoxicam), salicylates (acetyl salicylic acid, sulfasalazine) and the pyrazolones (apazone, bezpiperylon, feprazone, mofebutazone, oxyphenbutazone, phenylbutazone); (g) cyclooxygenase-2 (COX-2) inhibitors; (h) inhibitors of phosphodiesterase type IV (PDE-IV); (I) other antagonists of the chemokine receptors; (j) cholesterol lowering agents such as HMG-COA reductase inhibitors (lovastatin, simvastatin and pravastatin, fluvastatin, atorvsatatin, and other statins),

sequestrants (cholestyramine and colestipol), nicotonic acid, fenofibric acid derivatives (gemfibrozil, clofibrat, fenofibrate and benzaifibrate), and probucol; (k) anti-diabetic agents such as insulin, sulfonylureas, 5 biguanides (metformin), α -glucosidase inhibitors (acarbose) and glitazones (troglitazone and pioglitazone); (l) preparations of interferons (interferon alpha-2a, interferon-2B, interferon alpha-N3, interferon beta-1a, interferon beta-1b, interferon gamma-1b); (m) antiviral 10 compounds such as efavirenz, nevirapine, indinavir, ganciclovir, lamivudine, famciclovir, and zalcitabine; (o) other compound such as 5-aminosalicylic acid and prodrugs thereof, antimetabolites such as azathioprine and 6-mercaptopurine, and cytotoxic cancer 15 chemotherapeutic agents. The weight ratio of the compound of the present invention to the second active ingredient may be varied and will depend upon the effective doses of each ingredient.

Generally, an effective dose of each will be used. 20 Thus, for example, when a compound of the present invention is combined with an NSAID the weight ratio of the compound of the present invention to the NSAID will generally range from about 1000:1 to about 1:1000, or alternatively from about 200:1 to about 1:200. 25 Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

The compounds are administered to a mammal in a 30 therapeutically effective amount. By "therapeutically effective amount" it is meant an amount of a compound of Formula I that, when administered alone or in combination with an additional therapeutic agent to a mammal, is

effective to prevent or ameliorate the thromboembolic disease condition or the progression of the disease.

Dosage and Formulation

5 The compounds of this invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. They may
10 also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. They can be administered alone, but generally will be administered with a
15 pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage regimen for the compounds of the present invention will, of course, vary depending upon known
20 factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment;
25 the frequency of treatment; the route of administration, the renal and hepatic function of the patient, and the effect desired. A physician or veterinarian can determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of
30 the thromboembolic disorder.

By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to 1000 mg/kg of

body weight, or between about 0.01 to 100 mg/kg of body weight per day, or alternatively, between about 1.0 to 20 mg/kg/day. Intravenously, the doses will range from about 1 to about 10 mg/kg/minute during a constant rate
5 infusion. Compounds of this invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

Compounds of this invention can be administered in
10 intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal skin patches. When administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent
15 throughout the dosage regimen.

The compounds are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as pharmaceutical carriers) suitably selected with
20 respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be
25 combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the
30 oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Moreover, when desired or necessary, suitable binders, lubricants,

disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

Compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates, and crosslinked or amphipathic block copolymers of hydrogels.

Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 100 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active
5 ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose
10 derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed
15 tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain
20 coloring and flavoring to increase patient acceptance. In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions.

Solutions for parenteral administration may contain a
25 water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are
30 suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field.

Representative useful pharmaceutical dosage-forms for
5 administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of unit capsules can be prepared by filling standard two-piece hard gelatin capsules each
10 with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestable oil
15 such as soybean oil, cottonseed oil or olive oil may be prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules should be washed and dried.

20 Tablets

Tablets may be prepared by conventional procedures so that the dosage unit is 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of
25 microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Injectable

A parenteral composition suitable for administration
30 by injection may be prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution should be made isotonic with sodium chloride and sterilized.

Suspension

An aqueous suspension can be prepared for oral administration so that each 5 mL contain 100 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 mL of vanillin.

Where the compounds of this invention are combined with other anticoagulant agents, for example, a daily dosage may be about 0.1 to 100 milligrams of the compound of

Formula I and about 1 to 7.5 milligrams of the second anticoagulant, per kilogram of patient body weight. For a tablet dosage form, the compounds of this invention generally may be present in an amount of about 5 to 10 milligrams per dosage unit, and the second anti-coagulant in an amount of about 1 to 5 milligrams per dosage unit.

Where two or more of the foregoing second therapeutic agents are administered with the compound of Formula I, generally the amount of each component in a typical daily dosage and typical dosage form may be reduced relative to the usual dosage of the agent when administered alone, in view of the additive or synergistic effect of the therapeutic agents when administered in combination.

Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients.

For this reason, when the compound of Formula I and a second therapeutic agent are combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the

combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in
5 the intestines. One of the active ingredients may also be coated with a material which effects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released
10 component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric
15 release polymer, and the other component is also coated with a polymer such as a lowviscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating
20 serves to form an additional barrier to interaction with the other component.

These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single
25 dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

Obviously, numerous modifications and variations of
30 the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be

practiced otherwise that as specifically described herein.